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Review

Pleural effusion aetiology, presentation, treatment and outcome in haematological malignancies, IgG4-related disease, chronic myeloproliferative diseases, and haemoglobinopathias: a review

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Abstract. *Background and aim:* Pleural effusions (PE) can complicate the course of hematologic disorders (HD) and may arise in the form of malignant PE or as a consequence of non-neoplastic complications. While a certain amount of data has been published regarding infectious and iatrogenic HD-associated PE (HPE), no comprehensive review regarding the other types of HPE has ever been conducted. To address this issue, we performed a systematic review of the literature regarding HPE, focusing on the clinical and chemical characteristics of PE, therapeutic approaches and ì outcomes at the one-year follow-up. *Methods:* We conducted our review according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. *Results:* Overall, 283 manuscripts and 1216 cases were included. In summary, PE frequently signals an underlying HD, especially Hodgkin's lymphoma and IgG4-related disease; it mainly consists of exudate, although chylothorax is diagnosed in some cases. Although cytological examination has a discrete diagnostic yield, it is generally insufficient to render a definitive diagnosis; pleural biopsy remains an important diagnostic means in such cases. Invasive diagnostic procedures are not frequently performed because of an increased risk of haemorrhagic complications. The majority of PE are resolved by means of systemic therapy. When local treatments are attempted, the most frequently adopted procedures are evacuative thoracentesis and indwelling chest tube placement. *Conclusions*: This review highlights the need for well-designed prospective studies comparing diagnostic means and therapeutic interventions for HPE to increase the quality of available data. (www.actabiomedica.it)

Key words: pleural effusion, hematologic disorders, thoracentesis, lung ultrasound

Introduction

Pleural effusions (PE) are known to complicate the course of several haematologic disorders (HD). These so-called haematologic PE (HPE) may present as malignant pleural effusions (MPE), as a complication due to the infiltration of the disease itself (i.e. chylothorax), or occur secondary to extramedullary haematopoiesis. HPE may present at disease onset or during the clinical course of the disease.

While an amount of data, albeit limited, has been published regarding infectious and iatrogenic HPE, no comprehensive review regarding other types of HPE has ever been conducted. To address this, we performed

a review of the literature regarding HPE, focusing on the underlining HD, the clinical and chemical characteristics of PE, therapeutic approaches, and outcomes of patients with HPE.

Materials and Methods

We conducted our review according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (1).

Selection criteria

We considered all published cases of HPE as eligible for inclusion, except those due to infections and treatment-related toxicity. We excluded abstracts, letters, editorials, narrative reviews discussing previously published cases, and case series lacking sufficient clinical information.

Search strategy

A MEDLINE/PubMed search was conducted using the following terms: "(hematology) OR (hematologic) OR (lymphoma) OR (myeloma) OR (leukemia) OR (myeloid) OR (lymphoproliferative) OR (myeloproliferative) AND "pleural effusion" [Mesh]." We selected articles in English, French or Spanish. We conducted electronic and full-text searches of the literature published between January 1945 and March 2021.

Data extraction

All records were screened and selected independently by two authors (NC and AF). The inclusion criteria were broad: we considered any paper presenting a case of haematological PE as a pathology of interest; all adult, paediatric and pregnant patients were included. The following data were extracted from each case:

1. population: patients with an HD developing a PE at HD presentation or during the follow-up;
2. interventions: any intervention, including palliative care, chemotherapy, radiotherapy, evacuative thoracentesis, chest tube insertion, decortication, surgical procedures, administration of intrapleural therapy, and stem cell or bone marrow transplantation;
3. comparator: not applicable;
4. outcome: one-year survival.

HPE included the following: multiple myeloma-associated PE, acute leukaemia-associated PE; chronic leukaemia-associated PE (including both chronic myeloid and lymphocytic leukemias); Hodgkin's lymphoma associated PE, non-Hodgkin's lymphoma associated PE, thalassaemia related PE, chronic myeloproliferative disorder-related PE, IgG4-related disease-associated PE, and other types of HD-associated PE.
The data extracted from each selected paper included: author names, patient age and gender, PE appearance (at HD presentation or during the follow up), type of PE (exudate, transudate), PE side (bilateral, unilateral, left or right), chemical-physical PE analysis (when available), cytological examination, and treatment.
We excluded lecture presentations, posters, guidelines, systematic reviews, meta-analyses and editorials.

Statistical analysis

Given the descriptive nature of most of the papers included, we did not consider a quantitative summary to be feasible. Therefore, we used a descriptive approach to summarize the cases, dividing the cohort of cases included according to the haematological pathology described.

We performed basic descriptive statistics (mean, range and percentage) depending on the nature of the considered variable, i.e. depending on whether it was categorical or numerical. The normal values were determined from age-specific data accepted by current literature and laboratories. The data were processed using statistical software (SPSS version 18.0).

Results

Cohort characteristics

We selected 283 manuscripts for further analysis, which included 1216 cases of HPE. Fig. 1 shows the flow diagram applied for article selection. Table 1 summarizes the characteristics of the 1216 patients included.

The mean patient age was 50.8 years (range 2-98), and the majority of patients were male (57.3). The most frequent HDs occurring with PE were non-Hodgkin's lymphoma (430 cases, 34.8%), Hodgkin's lymphoma (272 cases, 22%) and multiple myeloma/plasmacytoma (228 cases, 18.5%). We also included 165 cases of acute leukaemia (13.4%), 49 cases of chronic leukaemia (4%), 28 cases of IgG4-related disease (2.3%), 25 cases of chronic myeloproliferative disorders (2%), 12 patients with thalassaemia (1%), 2 cases of Castleman's disease, 2 cases of post-transplant lymphoproliferative disorder (PTLD) and 3 cases of other types of HD (1 case of histiocytic sarcoma, 1 case of primary fibrous histiocytoma and 1 case of Rosai-Dorfman disease).

In 648 patients (61.9%), PE was already present at HD diagnosis. 389 out 610 studies (49.4%) did not report the side of the PE . PEs constituted exudates in almost all cases (174/176, 98.8%).

Non-Hodgkin's lymphoma (NHL)-associated PE

Our review included 430 cases of NHL-associated PE. The population had a mean age of 58 years (range 2-98 years), and were predominantly male (64%).

PE was already present at the diagnosis of NHL in exactly half of the cases (50%), being unilateral in 62.5%, and with no side predominance. In more than 90% of cases, the PE was exudate. Mean lactate dehydrogenase (LDH) was 1895.37 UI/L, mean protein concentration was 4.88 g/dL, and mean glucose concentration was 104.28 mg/DL; adenosine deaminase (ADA) levels were generally elevated (86.50 U/L).

In agreement with previously published case studies, cytological examination showed positivity for neoplastic cells in more than 64% of cases. Pleural biopsy was performed in 30 cases. Neoplastic cell infiltration was found in 22 cases (73.3%).

Overall, 90% of all patients with NHL-associated PE received treatment. More than 60% received combination therapy with chemotherapy and steroids. Evacuative thoracentesis was performed in 15% of cases, chest tube placement was required in 14.7%, and pleurodesis was performed in 8.7%. Decortication was performed in just a single case (0.4%). In 24% of the NHL patient cohort, bone marrow transplantation/stem cell transplantation (BMT/SCT) was attempted. A total of 13 patients (5.6%) underwent radiotherapy, and 6 received intrapleural medical treatment.

The outcome was reported for 266 patients , of which 55.6% were alive at the one-year follow-up.

Hodgkin's lymphoma (HL)-associated PE

We found 272 cases of HL-associated PE. The mean age of these patients 18 years (range 4-92), and the female gender was slightly more predominant (55.6%).

In 90% of cases, PE was present at the time of HL diagnosis. PE was unilateral in the majority of cases (66%). Right PE was more frequent (almost 80%) than left. PE was an exudate in 87.5% of cases. The results of cytological examination were reported in relatively few cases (35/272; 13%), e.g. and were significantly positive for neoplastic cells in 69% of these cases (9/13). In just a single case pleural biopsy did reveal neoplastic cell infiltration.

Complete chemical-physical composition data for the PE were lacking in all cases.

In just a single case was no treatment with curative intent provided. This was due to the patient's poor general condition. Almost all the treated patients received chemotherapy (99.5%) and steroids (98.6%). None underwent local interventional approaches. More than 97% of the patients were still alive at one-year follow-up.

Myeloma and plasmacytoma

Of the 228 patients affected by myelomatous effusions, 217 suffered from multiple myeloma , and the remaining 11 were diagnosed with plasmacytoma. The mean age was 59.6 years (range 4-92), and more than half of the patients were male (55.7%).

PE was already present at the time of HD diagnosis in 53% of the subjects, and unilateral effusion was predominant (67.3%). Interestingly, the left side was most frequently involved (63.8%). Overall, 90.9% of PE were exudates (their physical-chemical compositions were not elucidated).Cytological examination was reported in 140 cases, and revealed atypical plasma cells in 128 (91.4%). In 23 cases, pleural biopsy results

were also provided. In 18 of these (78%), plasma cell infiltration was found.

Overall, 87.3% of the patients underwent some form of treatment. Ninety-three patients (84.5%) underwent chemotherapy, 68 (61.8%) received steroids, and 10 (9.1%) underwent BMT/SCT. In 13 cases (11.8%), a chest tube was positioned, 8 patients underwent pleurodesis, and 1 received pleural decortication. In 7.3% of cases (8), repetitive evacuative thoracenteses were performed.

Outcome data were provided for 136 patients, of which 63% died within one year from the diagnosis.

Acute leukaemia (AL)

One hundred sixty-five patients affected by acute leukaemia (AL) and PE were included. The mean age of this patient population was 61.5 years (range 3-76), and 60% were male. PE was already present at AL diagnosis in 54.2% of cases. The effusion was unilateral in 72.4% of cases, with left predominance in 94%. Exudate was indicated in all of the cases for which the type of effusion was described (17 cases). Overall, PE LDH, proteins and ADA were elevated (mean values: 1613.3 UI/L, 5.22 g/dL, and 47.2 U/L, respectively). The mean glucose concentration was 111.63 mg/dL. In 90% of patients, cytological examination was positive for neoplastic cells. Pleural biopsy findings were reported for only 3 cases. None indicated neoplastic cell infiltration.

The treatment undertaken was described in only 19 cases (12%). Two patients underwent a conservative treatment strategy, with minimally invasive palliative measures, 155/17 patients (88.2%) received chemotherapy, and 12 (70.6%) received steroids. In 4 cases out 17(23.5%), a chest tube was positioned, and three patients (17.6%) required pleurodesis. In other 3/17 cases (17.6%), repetitive evacuative thoracentesis was preferred.

At one-year follow-up, 79%% of the patients for whom this datum was given (90/114) were still alive.

Chronic leukaemia (CL)

A total of 49 cases of CL-associated PE were identified. The mean age of the patients was 64.6 years (range 4-49), 57.1% of whom were male. The frequency at which PE presented at CL diagnosis compared with during follow-up was not statistically different (51% vs 40%). PE was predominantly unilateral (60.4%) and in the form of an exudate (81.2% of cases). Neoplastic cells were identified thanks to cytologic examination in 60.4% of cases where cytological analysis was provided. Just 3 papers reported pleural biopsy findings, and in all 3, atypical cells were identified by histological examination.

Pleural liquid composition was reported in a minority of the cases. The mean LDH value was 3139.46 UI/L, the mean protein concentration was 4-6 g/L, and the mean glucose value was 67.3 mg/dL. An elevated ADA value was reported in 4 cases (mean value: 390.7 U/L).

Details regarding treatment were provided for 22 patients. Two received no treatment. 15 underwent chemotherapy alone (68.2%),and 8 received chemotherapy in combination with steroids (36.4%). A chest tube was positioned in 4 cases (18.2%), and pleurodesis was performed 2 (9%). Radiotherapy was administered in 3 patients (13.6%). One patient (4.5%) received intrapleural methotrexate.

IgG4-related disease

We found 28 cases of IgG4-related disease-associated PE. The mean age was 70.5 years (range 43-84), and patients were principally male (89.3%). PE was present at IgG4-related disease presentation in 87.5% of cases, mainly as unilateral (60%,9/15) and on the right side (66.6%, 6/9). IgG4-related disease-associated PE was an exudate in 100% of the cases for whom this datum was given (13 cases). The histological findings on pleural biopsy were compatible with IgG4-related disease diagnosis in 19 out of 22 cases (86%).

In the majority of cases pleural fluid composition was reported. In 11 cases, LDH value was reported, with a mean value of 1072.45 UI/L; in 16 cases, protein concentration was reported, with a mean value of 3.92 g/dL).

The treatment administered was described for 12 (43%) of the 28 cases of IgG4-related disease-associated PE. All patients received systemic steroids. In 2 cases, chest tubes were required (both patients underwent pleurodesis, and one also underwent decortica-

tion). In one case, multiple evacuative thoracenteses were performed.
The outcome was reported for almost half of the cases (13/28). Of these, 66.7% did not survive until one-year follow-up.

Chronic myeloproliferative disorders

The literature reported 25 cases of chronic myeloproliferative disorder (CMD)-associated PEs. The mean age was 63.16 years (range 33-78), 56% of which were male. The majority of the PE appeared during the course of CMD (68%), principally as unilateral effusions (69.6%), 56.2% of which were on the left side.

Effusions were all exudates. Thirteen cases (54.17%) presented atypical myeloid cells upon cytological examination. The result of pleural biopsy was reported for 4 cases, and in 3 of these neoplastic cell infiltration was found.

The treatment undertaken was reported for 4 patients (16%). In 1 case, no treatment was carried out due to the patient's poor performance status. A chest tube was positioned in 2 cases. Two patients received chemotherapy and steroids, and 1 patient underwent tetracycline pleurodesis.
Of the 21 patients whose outcome was reported, 20 (95%) did not survive until the one-year follow-up.

Thalassaemia

Intrapleural extramedullary haematopoiesis (EMH) due to alpha or beta thalassaemia was found in 12 patients, almost 60% of whom were male, with a mean age of 43.9 years (range 29-56). PE was already present at HD diagnosis in 68.3% of cases. Effusion was unilateral in 66.7% of the cases (8/12) with no side predominance. Effusion was exudate in 100% of cases, with a mean LDH value of 756.6 UI/L, a mean protein concentration of 4.32 g/dL, and a mean glucose concentration of 68 mg/dL. In a single case, pleural biopsy results were reported and showed non-specific chronic inflammation.

Data regarding treatment were provided for all patients, and was mainly based on was mainly based on steroids (54.5%) and hydroxyurea (72.73%). Five patients (45.5%) underwent chest tube insertion, and 4 underwent pleurodesis with tetracycline or bleomycin. Overall, 70% of the patients were still in follow up at one-year follow-up.

Other haematological disorders

Our analysis included 2 cases of Castleman disease, 2 cases of PTLD, 1 case of histiocytic sarcoma, 1 case of primary fibrous histiocytoma, and 1 case of Rosai-Dorfman disease. The majority of these patients (85.7%) presented PE at HD diagnosis. All cases were unilateral. Six cases reported the side of PE, of which 5 were on the right side.

Pleural fluid composition was described in 2 cases (both were exudates). In 5 out 6 cases, neoplastic cells were found following cytologic examination.

Pleural biopsy was performed in 2 cases: in one, histological examination showed diffuse sheets of neoplastic cells compatible with the diagnosis of primary mediastinal histiocytic sarcoma; in the other, which revealed a fibrous histiocytoma, the pleural biopsy revealed giant multinucleated cells. In this patient, the diagnosis was formulated from the results obtained from a vertebral biopsy.

All of the treated patients received chemotherapy, and 2 of them also received systemic steroids. None of these patients underwent local procedures. The outcome was reported for all patients, 4 of whom (50%) died within a year.
A table providing all details of our analysis can be found in Supplementary Material 1 (Appendix).

Discussion

Every day, clinicians are faced with PEs of unknown origin. The aetiology of PEs may vary according to the series of cases presented to individual centres, but malignant effusions consistently represent a considerable percentage of all cases (2). It is not uncommon for PE to be the first signal of an underlying HD, or, albeit more rarely, a complication during the course of a pre-existing HD.

Even in malignant disease, PE can present as a reactive effusion with no malignant elements. Non-

neoplastic effusions might result from a number of different mechanisms, including: venous compression, lymphatic obstruction due to enlargement of the pulmonary and mediastinal lymph nodes, urinary tract compression, reactive pleuritic, and EMH (3-5).

The size of HD-associated PE can vary considerably, ranging from minimal costophrenic angle blunting to massive effusions (6).

HPA diagnosis is generally easily accomplished through common radiological techniques, such as computed tomography (CT), chest X-ray and thoracic ultrasound (TUS). TUS, in particular, not only allows a bedside diagnosis, but also provides safe and affordable guidance for pleural tap and drainage procedures, especially relative to small-bore indwelling catheters (7-8).

HD-associated PEs are generally exudates and arise independently of the underlining disorder. In some cases (predominantly lymphomas and AL), chylothorax is diagnosed (9-12). Data from single cohorts reported an overall incidence of chylothorax in malignant HD of around 20% (13-20). Urinothorax was diagnosed in a single case, probably due to large abdominal lymphomatous masses causing a ureteral obstruction (21).

PE has been reported in up to 20% of NHL and 30% of HL, mainly in MPE (3-5-22). Cytological examinations were positive for malignant cells in 70% and 64% of patients with HL and NHL, respectively (5). However, PE frequently contains only sparse malignant cells, so that the diagnostic yield of cytological examination strongly depends on the cytologists' experience. Hence, cytology is insufficient to render a definitive diagnosis as a stand-alone test (23). Pleural biopsy remains another important diagnostic means in such cases. However, it is rarely performed, as the majority of the diagnoses result from lymph node examination.

AL-associated PE is also not uncommon. The majority of AL-associated PE are non-malignant. According to a large case series, infection is the most common cause of AL-associated PE, followed by leukaemia and volume overload (24). AL involvement of the pleura generally results in an extramedullary proliferation of clonal cells. Leukaemic infiltrates in the pleura have been found as a complication of systemic leukemic relapse and in the form of an isolated site of relapse, even during complete bone marrow remission (16-25). In our review, 90% of the analyzed pleural effusions presented leukaemic clones upon cytologic examination. AL involving pleura are more frequently lymphocytic AL than nonlymphocytic AL.

Pleural involvement in CL is uncommon. According to previous reports, pleural involvement is diagnosed in 7% of CL cases (26). In half of the cases, CL-associated PE presented at CL diagnosis; in the other half, PE were found in patients with a long-standing diagnosis of CL (27). PE can result from infection, primary pleural leukaemic involvement, lymphatic obstruction, synchronous cancer, and drug toxicity. The cytological and chemical-physical examination of PE are useful means to guide differential diagnoses (28). Neoplastic cells were identified through cytology and immunophenotypic analysis in 60% of cases. Pleural biopsy is rarely performed; however, it is strongly encouraged when differential diagnosis with tubercular pleuritis is required. In 80% of pleural effusions due to tuberculosis, histological examination of pleural biopsy shows granuloma (29). According to our findings, in 75% of biopsies from CL-associated PE, histology revealed leukaemic infiltration.

PE in CMD is rare and generally related to chronic myelomonocytic leukaemia (CMML) (30-31). The primary cause PE in CMD is an infection, followed by infiltration of leukaemic cells into the pleura (24-31). Furthermore, PE has been described in 10% of CMD's related to autoimmune phenomena (32).

Although PEs in multiple myeloma (MM) are relatively common (6% according to current literature), less than 1% of the cases are consistent with myelomatous effusions, principally lgA-MM. The majority of MM-related PE occur as a consequence of infections, or heart and renal failure (33-35). According to Rodriguez et al., in order to formulate the diagnosis of myelomatous effusion, three criteria should be met: a cytological examination of pleural effusion positive for atypical plasma cells, histological examination of pleural biopsy compatible with malignancy, and demonstration of monoclonal proteins in the PF through electrophoresis (34-36). According to the reported data, cytology results are diriment in 90% of cases of neoplastic MM-associated PE. When performed

(23/238), pleural biopsy shows a high diagnostic yield (almost 80%). However, myelomatous involvement of the pleura is often discontinuous; hence, it is not always diagnostic.

EMH occurs as a response to chronic non-malignant haematologic conditions or as a consequence of bone marrow infiltration (e.g. myelofibrosis) (37). EMH might involve several organs, including serous surfaces. Intrapleural EMH has been reported in various haemoglobinopathies (principally thalassaemia) and myelofibrosis (38-40). According to the published literature, PE due to EMH is almost always exudative and generally occurs as a unilateral effusion, with a similar frequency for both the left and right side (38). PE cytology provided diagnostic results in more than half of the cases, while biopsy showed pleural infiltration with EMH in most cases. However, thoracoscopy and biopsy are rarely performed due to the high risk of haemorrhagic complications (40).

According to the largest case series, IgG 4-related disease involves the lung in 14% to 54% of cases, in the form of airway obstruction, parenchymal masses and pleural effusion (41-43). Pleural disease in these patients generally consists of massive PE or pleural nodular lesions. In such cases, pleural cytology is irrelevant. Histological examination of the pleura generally shows fibrinous exudates, chronic inflammation, fibrosis and lymphoplasmacytic infiltration (44-45). Although these findings are peculiar, they are not specific for diagnosing IgG4-related disease, especially when there is no other disease localization elsewhere. It has been suggested that, in order to support the diagnostic hypothesis of IgG4-related disease, plasma cell infiltrations should represent 50% of inflammatory infiltrates with endothelium in the pulmonary vasa. Furthermore, IgG4-positive cells should account for almost 30% of IgG-positive cells on immunohistochemical analysis (44-46).

Overall, chemical-physical examination plays a fundamental role in the diagnostic evaluation of PE of unknown origin. Standard biochemical pleural fluid analyses include pH, LDH, total protein, glucose, ADA and a cell count.

ADA activity is noteworthy. ADA is often found to be elevated in infectious PE (e.g. tubercular pleuritic) and neoplastic PE, including several HD.

Pleural fluid cytology and special immunohistochemical analyses also constitute fundamental steps in the diagnosis. The majority of PE due to malignant HD present positive cytology. Occasionally, positive cytology findings of a diagnostic thoracentesis may lead to an underlying HD being discovered (47). However, although the cytological analysis may support the diagnosis, it may not be sufficient alone. In our analysis, cytologic diagnostic yield broadly varies according to the disease involved, with the highest diagnostic rates in MM (90% of positivity).

In PE of unknown origin, histological analysis of pleura obtained through pleural biopsies is strongly recommended, especially when the cytology is non-diagnostic (48-49). Video-assisted thoracoscopy (VATS) or ultrasound-guided pleural biopsy could reasonably be applied when imaging findings suggest pleural involvement (e.g. pleural thickening, nodules) (50).

Nevertheless, most of the patients affected by HD-associated PE do not undergo thoracentesis or pleural biopsy because they tend to present other evidence or lymph nodal or bone barrow disease for diagnostic and staging purposes. Furthermore, invasive procedures, such as thoracentesis, thoracoscopic and surgical biopsy, could be challenging because of a high risk of complications due to haemorrhagic diathesis or reduced platelet count (24-51). In our opinion, this is the main reason for the paucity of data regarding cytological and histological features of HD-related PEs.

In the case of a known HD with concomitant PE, when all the possible causes of pleural effusion have been excluded, the most likely cause of the effusion is the systemic manifestation of the underlying HD. The management of HD-associated PE can be challenging. The majority of these PE resolve with systemic therapy. Indeed, in almost all the reported cases, systemic treatment with or without a local evacuative procedure was attempted. The majority of the patients who underwent only palliative care were in the MM cohort (almost 13%), presumably due to advanced age and an overall poor general condition. When local treatment was performed, the most frequent procedures were evacuative thoracentesis and indwelling chest tube placement.

It should be emphasized that due to the high risk of infection and bleeding, invasive approaches were

often deferred in the past whenever possible (52-54). Indeed, chest tube placement has only become a first-line therapy for the management of HE-associated effusions during the last decade, especially when the HE is malignant in aetiology (13-55). Indwelling pleural catheters could be combined with pleurodesis or the administration of various intrapleural drugs (steroids, chemotherapy or immunomodulant treatments). Although anecdotal experiences have reported potential benefits of local chemotherapy in terms of disease remission, the main purpose of the local strategy is to relieve symptoms (55-58).

Real-life prospective studies analyzing the real benefits of local treatments for HD-associated PE are lacking.

In our cohort, high rates of death within one year of follow-up were found, especially in relation to AL and CML.

No prognostic role of PE on the course of HD has been defined. PE presenting at the diagnosis of a HD, or emerging soon after its first presentation, has been suggested to correlate with highly aggressive disease (3-59-60). However, it should be said that these assumptions result from a very small number of observational studies, case reports, and retrospective case series.

In Faiz's retrospective analysis, no significant correlation between the number of pleural procedures and PE volume with overall survival was found. On the other hand, a direct correlation between AL status and the first pleural procedure was identified. Therefore, the authors speculated that PE appearance early after AL diagnosis might predict a more aggressive disease form (13).

A case-controlled study conducted on 70 patients with NHL and categorized according to grade (based on the Working Formulation) found that PE at the time of presentation does not negatively influence the response to treatment and overall survival of patients with intermediate and low-grade NHL (16). In our cohort, 60% of patients were dead at one-year follow-up.

In our opinion, the recently validated scoring tool – the LENT score – is the only risk stratification system able to predict survival in patients suffering from MPE. According to this system, patients with a high LDH in their pleural fluid, a high Eastern Cooperative Oncology Group (ECOG) performance score (PS) and a high neutrophil-to-lymphocyte ratio are those with the highest risk of death (61). However, the cohort used in the LENT scoring system validation process was relatively small, and thus constitutes a limitation that remains to be resolved. Indeed, the role of this scoring system was recently questioned (62).

Conclusion

Pleural effusions in patients with HD can occur as either the dissemination of a malignant process or as a non-neoplastic complication, such as lymphatic obstruction, a reactive process, infection, volume overload or drug toxicity.

Effusions of unknown aetiology should never rule out the PE diagnostic hypothesis, especially when recurrent, and independently of whether they are neoplastic or non-neoplastic. PE may present at any time over the course of a haematological disorder. However, in Hodgkin's lymphoma and IgG4-related disease, PE is more frequently present at the onset of HD. When feasible, a diagnostic thoracentesis should be performed in order to investigate the nature of the effusion. In cases of elusive cause, pleural biopsy should be considered. The lack of prospective studies comparing local and systemic treatments represents a major obstacle to the development of standards of care for PE.

Conflicts of interest: Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article.

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