Review Article

Characteristics of pleural effusion due to amyloidosis

Cristina Pou[1], Lucía Ferreiro[2,3], Juan Suárez-Antelo[2], Antonio Golpe[2,3], José M. Álvarez-Dobaño[2,3], María Elena Toubes[2], Adriana Lama[2], Nuria Rodríguez-Núñez[2], Jorge Ricoy[2], Carlos Rábade[2], Tamara Lourido[1], Luis Valdés[2,3]

[1]Department of Pulmonology, Álvaro Cunqueiro University Teaching Hospital, Vigo, [2]Department of Pulmonology, University Clinical Hospital of Santiago de Compostela, Santiago de Compostela, [3]Interdisciplinary Research Group in Pulmonology, Health Research Institute of Santiago de Compostela (IDIS), Santiago de Compostela, Spain

Address for correspondence:
Dr. Lucía Ferreiro, Department of Pulmonology, University Clinical Hospital of Santiago de Compostela, Travesía da Choupana s/n, Santiago de Compostela 15706, Spain.
E-mail: lferfer7@gmail.com

Submission: 15-12-2022
Accepted: 01-02-2023
Published: 25-04-2023

Abstract:

The characteristics of patients with pleural amyloidosis (PA) are poorly known. A systematic review was performed of studies reporting clinical findings, pleural fluid (PF) characteristics, and the most effective treatment of PA. Case descriptions and retrospective studies were included. The review included 95 studies with a total sample of 196 patients. The mean age was 63 years, male/female ratio was 1.6:1, and 91.9% of patients were >50 years. The most common symptom was dyspnea (88 patients). PF was generally serious (63%), predominantly lymphocytic, and with the biochemical characteristics of transudates (43.4%) or exudates (42.6%). Pleural effusion was generally bilateral (55%) and <1/3 of the hemithorax (50%), although in 21% pleural effusion (PE) exceeded 2/3. Pleural biopsy was performed in 67 patients (yield: 83.6%; 56/67) and was positive in 54% of exudates and 62.5% of unilateral effusions. Of the 251 treatments prescribed, only 31 were effective (12.4%). The combination of chemotherapy and corticosteroids was effective in 29.6% of cases, whereas talc pleurodesis was effective in 21.4% and indwelling pleural catheter in 75% of patients (only four patients). PA is more frequent in adults from 50 years of age. PF is usually bilateral, serous, and indistinctly a transudate or exudate. A pleural biopsy can aid in diagnosis if effusion is unilateral or an exudate. Treatments are rarely effective and there may be definitive therapeutic options for PE in these patients.

Keywords:

Amyloidosis, pleural effusion, pleural fluid

Amyloidosis is a heterogeneous group of diseases in which normally soluble plasma proteins are deposited in the extracellular space in an abnormal insoluble fibrillar form.[1,2] The deposition of these proteins may disrupt the function of the organs affected. The most frequent forms of amyloidosis include the deposit of an abnormal protein (i.e. hereditary amyloidosis, systemic acquired light chain amyloidosis [amyloid light chain (AL)]); excess deposition of a normal protein (i.e. reactive systemic amyloidosis [AA], hemodialysis-related beta-2 microglobulin amyloidosis), whereas some have an unknown etiology (i.e., transthyretin amyloidosis in its normal form [wild type], also known as senile amyloidosis, or amyloidosis related to atrial natriuretic peptide).[2] The type of amyloid protein that builds up (around 30 have been described)[3] provides information about the organ affected and natural course of the disease and provides guidance about the therapeutic options available.

Primary systemic amyloidosis has a low incidence. In a review conducted between 1950 and 1989, the general incidence adjusted for sex and age ranged between 6.1 (1950–1969) and 10.5 (1970–1989) cases/million people/year.[4] Estimating the prevalence of pleural effusion (PE) in patients with systemic amyloidosis is challenging. In a series of 636 patients with

Access this article online

Quick Response Code:

Website: www.thoracicmedicine.org

DOI: 10.4103/atm.atm_433_22

How to cite this article: Pou C, Ferreiro L, Suárez-Antelo J, Golpe A, Álvarez-Dobaño JM, Toubes ME, *et al.* Characteristics of pleural effusion due to amyloidosis. Ann Thorac Med 2023;18:53-60.

amyloidosis followed up for 7 years, 6% exhibited large persistent PE, whereas PE was mild in 10%–15% of patients.[5] In contrast, in a study performed over 88 years involving 223 autopsies of patients with amyloidosis, no cases of pleural involvement were documented.[6] In the 1977–2004 period, a total of 23 cases of amyloidosis complicated with PE were reported in the scientific literature in English, of which 21 patients presented pleural amyloid infiltration.[5]

The aim of this systematic review was to document the clinical, radiological, and pleural fluid (PF) characteristics of patients with systemic amyloidosis complicated with PE, and evaluate the most effective approach to recurrent symptomatic PE.

Methods

A systematic review methodology based on the principles of the PRISMA study[7] was used. As we did not find a series large enough within the scope of this study, all the cases described in the literature were included.

Selection criteria

Inclusion criteria were all cases of amyloidosis and PE (pleural amyloidosis [PA]) of any age, irrespectively of the type of publication, except for abstracts of communications presented in conferences and editorials, reviews, or letters to the editor that did not report a new case.

Sources of information

Several public databases were searched by year of publication. Full-text articles in English, Spanish, French, Italian, or Portuguese were reviewed. A literature search was performed on the following online databases: Medline (through Pubmed interface), Embase, Scopus, and Web of Science. The literature search was carried out between January 1 and September 15, 2021. The following search terms were used following adaptation to each database: "amyloidosis" AND "PE." In addition to the electronic databases consulted, a manual search was performed of the reference lists of the articles included.

Data collection process

Data from selected studies were extracted electronically (Microsoft Excel 2016, Microsoft Corp, USA). The information collected included: authors, year of publication, number of cases in the series, age, gender, type of amyloidosis, cough, dyspnea, chest pain, laterality and size of PE, recurrence of PE, appearance of PF, description of whether it is a transudate/exudate, number of red blood cells and leukocytes/mm^3, lymphocyte percent count, segmented and mononuclear cells, total protein and lactate dehydrogenase (LDH) ratio in PF/blood (S), LDH in PF, triglycerides, pleural biopsy results (and type of biopsy used to establish a diagnosis), treatments received and patient's response, complications, and final outcomes.

Methodological quality of individual studies

Since only one or a few cases were reported in the articles reviewed, their quality was not evaluated in relation to study type, internal validity, generalizability, heterogeneity, and precision.

Outcomes of interest

The measures of interest included the demographic characteristics of patients, clinical symptoms, associated diseases, biochemical behavior of PF, patient's response to the different treatments established, and final clinical outcomes.

Statistical analysis

Due to the wide heterogeneity and descriptive nature of the studies, a simple descriptive analysis (proportion, median, and range) of each outcome of interest was performed.

Results

A total of 95 articles published over a period of 63 years were included, representing a final sample of 196 patients with PA. Figure 1 shows the flow chart of the article selection process.[8-102]

Clinical and demographic characteristics

Table 1 provides a description of the clinical and demographic characteristics of the 196 patients included in the study. Figure 2 presents the age distribution. The mean age was 63 years (range, 16–92), though this

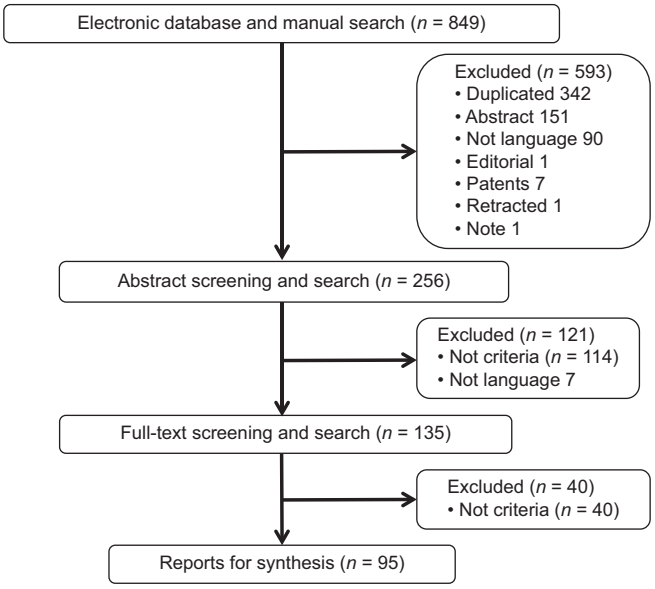

Figure 1: PRISMA flowchart of evidence synthesis

information was only available for 148 patients (75.5%). Although PA was identified in some patients in the second decade of life, it was more frequent in patients of advanced age (91.9% [136/148] were older than 50 years). The majority of patients were male (87/142; 61.2%). The most frequent respiratory symptoms included dyspnea (88 patients), chest pain, and cough (20 each) [Table 1]. There are limited data for the 54 patients of the Binder series,[95] since this group was extracted from a larger series that also included cases of pericardial effusion.

Diagnosis

Only nine cases[10,30,35,77,78,82,83,90,94] (4.6%) met the diagnostic criteria for primary amyloidosis (plasma cell proliferation, organ damage related to amyloidosis, positive Congo Red amyloid staining in some tissue, and evidence of amyloid light chain on electron microscopy).[10] Pleural biopsy was performed in 67 patient [(28 by closed pleural biopsy[18,30,33,34,38,39,41,42,45,47,49,55,60,61,88] and 30 by pleuroscopy (medical or surgical)[8-10,20,29,30,37,41,51,55,62,65,72,73,75,76,78,79,81,83,84,87,88,90,92,93,97,99], in 9 cases the type of biopsy was not detailed.[14,22-24,67,70,74,96,98]] Amyloid PE was confirmed in 56 patient [21 by closed pleural biopsy[18,30,33,34,42,45,47,49,60,61] and 29 by pleuroscopy;[8-10,20,29,30,37,41,51,55,62,65,72,73,75,76,78,79,81,83,87,88,90,92,93,97,99] the type of biopsy was not available in 6 cases (12%).[22-24,58,91,96]] The diagnostic performance of closed pleural biopsy and pleuroscopy was 75% (21/28) and 96.7% (29/30), respectively. Table 2 shows the etiology of all cases of amyloidosis complicated with PE, number of patients with pleural involvement, and the type of diagnostic biopsy employed.

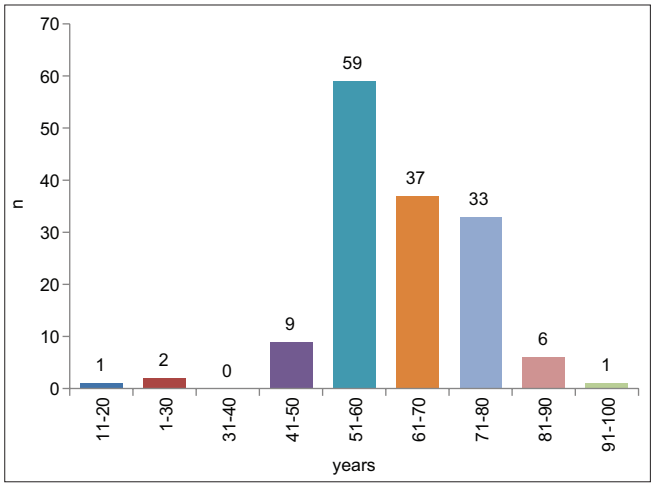

Figure 2: Age group distribution of patients with pleural amyloidosis

Table 1: Demographic and clinical findings of patients with pleural amyloidosis

Characteristics	Data	Comments
Age, years (196 cases), median (range)	63 (16-92)	Although the age of one patient was 16 years[24], 91.9% of patients (136/148) were older than 50
Gender (male/female)	87/55	Proportion 1.6/1
Dyspnea (yes/no)	88/0	In 108 cases it was not clear whether patients had dyspnea
Cough (yes/no)	20/1	No cough[13]
Chest pain (yes/no)	20/5	No chest pain[13,15,69,71,98]

The most frequent forms of amyloidosis were primary systemic amyloidosis (138; 70.4%), senile amyloidosis (32; 16.3%), and reactive systemic amyloidosis (16; 8.2%). Amyloidosis secondary to hemodialysis[55] and hereditary amyloidosis[8] were considered separately. In 7 cases (3.6%) the type of amyloidosis was not mentioned.[15,17,75,86,87]

Pleural effusion

PE was bilateral in 59/107 patients (55%), right sided in 36 (34%)[8,9,11,14,17,20,22,27,29,32-34,37,41-43,45,48,51,55,56,65,67,76,79,83,86,88,91,94,99,101] and left sided in 12 (11%).[13,23,24,30,35,38,46,60,69,81,97] PE was not identified as unilateral or bilateral in 89 cases (45%). The size of PE was documented in 92 cases (47%). PE was small in 46 patients (50%) (<1/3 of the hemithorax), moderate in 27 (30%) (>1/3 and <2/3 of the hemithorax), and large in 19 (21%) patients[17,19,30,33,35,40,43,46,50,59,64,72,76-78,80,81,92,94] (>2/3 of the hemithorax).

Diagnostic thoracentesis was performed in 122 patients (62.2%). PE appearance was described in 44 cases (22%): PF was serous in 28 (63%), milky in 6 (14%),[10,21,48,54,61,91] hematic in 6 (14%)[27,30,31,55,81] and serohematic in four patients (9%).[44,76,77,86] The smell of PE was not described in any fluid. The biochemical characteristics and nucleated cell count in PF were available for 95 cases (48.5%) [Table 3]. Lymphocyte count was >50% in 44% of patients (30/68). In accordance with Light criteria, PF was a transudate in 53 cases (43.4%) and

Table 2: Etiology of pleural amyloidosis

Type of amyloidosis	*n*	Pleural involvement (*n*)	Closed biopsy (*n*)	Pleuroscopy (medical or surgical) (*n*)	Unknown type of biopsy*	Necropsy
Hereditary	1	1	0	1		0
Primary systemic	138	41	19	17	5	0
Reactive systemic	16	9	2	6	1	0
Senile	32	0	0	0		2
Hemodialysis	2	2	0	2		0
Not described	7	3	0	3		0

*Studies do not mention what type of pleural biopsy was done

Table 3: Descriptive analysis of the parameters determined in pleural fluid

Parameter	*n*	Median	Range	Comments
Red blood cells	44	1710	30-25,200	Only one patient presented a red blood cell count>10,000 cells/mm^3[41]
Nucleated cells (cells/mm^3)	63	4115	21-180,000	Only 6 patients presented>5000 cells/mm^3[14,30,35,49,55,73]
Differential count				
Lymphocytes	68	54%	10%-99%	30 (44.1%) patients presented a lymphocyte count >50%
Polymorphonuclears	49	13%	1%-80%	Only 1 patient had a polymorphonuclear count >50%[92]
PF proteins (g/dL)	43	3	0.4-6.9	In 19 cases (41%) protein values were ≥ ng/dL
PF/S protein ratio	77	0.38	0.1-1.4	In 13 patients (17%) PF/S protein ratio was>0.5[18,30,33,34,36,37,42,48,68,73,74,93]
PF LDH (IU/L)	76	342.1	0.38-13,740	In 15 cases (19%) LDH was ≥200[10,33,34,36,37,41,42,45,48,55,61,73,92]
P/S LDH ratio	62	61.3	0.12-106	In 16 cases (25.8%) P/S LDH was ≤0.6[8,10,30,33-36,41,45,54,64,66,68,80]
Triglycerides	8	190.3	1-391	5 cases with triglycerides ≥110 mg/dL[10,21,61,68,74]
Cholesterol	8	37.6	1-103	Only one case presented>55 mg/dL[68]
Cytology	75			Diagnosis was based on analysis of the PF cell block in 2 cases[58,91]
Culture	48			Negative in all cases

LDH=Lactate dehydrogenase, PF=Pleural fluid, PF/S ratio=PF/serum ratio

an exudate in 52 (42.6%) cases.[103] This information could not be obtained for 17 patients (13.9%). Of the six patients with a milky PF, triglycerides were only determined in 4 (values of 391, 300, 104, and 110 mg/dL).[10,21,54,61] PF culture was performed in 75 cases (38%) and was negative in all. Cytology was described in 48 patients (24%). In two cases, the diagnosis was established based on the analysis of the PF cell block.[58,91]

Of the 52 cases where PF was identified as an exudate, 28 (54%) exhibited pleural involvement. Pleural biopsy of the 48 cases with unilateral PE demonstrated pleural amyloid infiltration in 30 (62.5%). Of them, according to Light criteria, 15 were exudates, 9 were transudates, and type of effusion was not described based on light criteria in 6 cases.[103]

Treatment of pleural effusion

In relation to the management of PE and its symptoms, we identified 251 treatments classified into 51 different therapeutic options. Response to treatment was defined as the total or partial control of PE or its symptoms. Only 31 (12.4%) patients showed good response to treatment (6 with the first treatment administered,[15,20,32,44,54,83] 14 with the second,[8,11,38,43,46,58-60,77,79,80,84,86,96] 6 with the third[10,47,51,63,78] and 5 with the fourth treatment administered[28,40,48,66,67]). Table 4 details the most frequent treatments or procedures (used in at least five cases). Only 7 options exceeded this cut-off value, accounting for 77.7% of the treatments established (195). Only 13 patients (6.7%) benefited from these treatments.

Therapeutic thoracentesis, alone or associated with diuretics, was the most frequently used treatment (40 and 48 times, respectively). This treatment was not effective for PE control, although the response to the first treatment was not documented in four cases. Diuretics in monotherapy were used in 32 patients, but they were effective only in one patient.[15] The combination

Table 4: Treatments administered to of pleural effusion associated with amyloidosis

Treatment	*n*	Favorable*	Unfavorable*	Unknown
Therapeutic thoracentesis	40	0	36	4
Thoracic drainage	26	0	23	3
Diuretics	32	1[15]	31	0
Thoracentesis + diuretic	48	0	48	0
Antibiotic	8	1[11]	6	1
Chemotherapy + corticosteroids	27	8[10,44,46,60,80,83,84,86]	12	7
Pleurodesis¶	14	38,47,51	2	

*Favorable: Full or partial control of pleural effusion or its symptoms; unfavorable: No control of pleural effusion or its symptoms or recurrence, ¶Different types of talc

of chemotherapy and systemic corticosteroids was administered to 27 patients. Eight patients improved (29.6%),[10,44,46,60,80,83,84,86] progress was not reported in seven cases. Chest drainage was performed in 26 patients, without any patient having obtained a clinical benefit. Talc pleurodesis was performed in 14 patients, with three patients having.[8,47,51] Finally, of the eight patients who received antibiotics in monotherapy, only one had a good response.[11] Other combination treatments were effective in 18 patients.[20,28,32,38,40,43,48,54,58,59,63,66,67,77-79,96] Indwelling pleural catheter (IPC), alone or associated with another treatment, was used in four patients, with a favorable response in three patients.[28,63,79]

The incidence of treatment complications was low (15 cases). Two patients had infection (empyema after pneumonectomy due to giant amyloidoma[22] and chest wall cellulitis related to IPC, with good response to oral antibiotic therapy[28]), and pneumothorax was documented in 13 patients.[19,47,50,96] In one case there are doubts as to whether pneumothorax was actually a complication of the treatment or of the disease (as the authors describe).[10]

Discussion

The majority of publications about PA only report a case or few cases (between 1 and 5 cases), except for two articles, which report 35[47] and 54[95] cases, respectively. For this reason, assessing the clinical characteristics of patients, course of PE, or the most effective treatments is challenging. This systematic review is aimed at shedding light on these questions.

Primary systemic amyloidosis is the form where more cases of PE were reported (41/138: 29.7%): however, the form of amyloidosis that proportionally causes more cases of pleural involvement is reactive systemic amyloidosis (9/16: 56%). The pathophysiology of PE in patients with amyloidosis is unclear, and several mechanisms could be involved: First, the deposition of amyloid substances on the surface of the parietal pleura may cause the build-up of fluid in the pleural space.[8,9] Amyloid deposits may also cause restrictive cardiomyopathy, which may induce PE derived from increased hydrostatic pressure within the pleural capillaries. Moreover, patients with primary systemic amyloidosis may develop chylothorax,[10] probably due to the deposition of amyloid substance in the lymph nodes. These three settings can be distinguished through PE analysis (exudates in the first option, transudates in the second option with elevation of natriuretic peptides, and triglycerides >110 mg/dL in the last option) or by ultrasonography or a pleural biopsy. Identifying transudates and exudates in this type of systematic review is difficult since the appropriate tests were not always ordered; 25% of transudates could have been mistaken for exudates, especially in patients receiving diuretic treatment;[104] the PF of PA has no specific characteristics, and natriuretic peptide determination and ultrasound data are rarely documented. However, PE can be useful to demonstrate pleural involvement, as it has a good diagnostic performance (56/67; 83.6%. Pleuroscopy has a better diagnostic performance than closed biopsy [96.7% vs. 75%, respectively]). The drawback is that pleuroscopy is rarely performed (67/196; 34.2%).

The radiological characteristics of PA are very similar to those of PE secondary to heart failure; thus, PA is generally bilateral (55%), rarely left-sided (11%), and usually small-sized (<1/3 of the hemithorax in 50% of cases). PF is normally serious, except for chylothorax, which PF has a milky appearance. Its smell has never been described, which suggests that it does not have any special characteristics. Determining whether PF is a transudate or an exudate is controversial. Unfortunately, the results of this study do not shed light on this question, as similar percentages were obtained. PF being a transudate or an exudate is probably related to the organ affected by amyloidosis. When amyloidosis involves the heart, it is a transudate and would cause heart failure. Conversely, when amyloidosis involves the pleura, it is an exudate. However, some authors postulate that amyloid deposits in the pleura are an incidental finding and do not play any role in the pathogenesis of PE.[33] This theory is refuted by the fact that a significant proportion of PEs with amyloid deposits in the pleura are exudates. In our opinion, amyloid pleural deposits should only be considered incidental findings in patients without PE. To the best of our knowledge, such event has never been reported. Nucleated cell count shows that PF usually is lymphocyte-rich (44% with more than 50% of lymphocytes), a characteristic shared by PEs related to heart failure or long-standing exudates. PF cytology and culture were generally negative, and the diagnosis was determined by cytology of the cell block of the PF in two cases.[58,91] Pleural biopsy has a high diagnostic performance when it comes to demonstrate pleural amyloid infiltration in unilateral PE and exudative effusions (62.5% and 54%, respectively), which supports its use on suspicion of PA.

Approaches to PE related to amyloidosis are very heterogeneous (51 different therapeutic options were identified) and poorly effective in reducing the size of PE or its symptoms (12.4%). The most effective treatments were systemic administration of chemotherapy and corticosteroids (29.6%) and talc pleurodesis (21.4%). The management of PE with an IPC alone or associated with other treatments also had very positive outcomes (75%) but was only used in four patients. In the light of these findings, talc pleurodesis or IPC emerge as the definitive therapeutic options for PA. The only complications of this treatment are related to the management of PE (infections or pneumothorax) and are unrelated to adverse events of systemic treatments.

Our review has some limitations. The main limitation of the articles reviewed is that they are case reports documenting one or a few cases, while others are comparative trials. Therefore, it was not possible to assess the quality of the original studies in terms of internal validity, generalizability, and precision. The studies available adopt very different approaches, with some placing the focus on the clinical characteristics of patients, whereas others hone in on diagnostic or therapeutic aspects. Detailed data could not be collected due to the heterogeneity of studies. Therefore, it was not possible to classify some effusions or determine the patient's response to a specific treatment. As it occurs with all rare diseases, publication bias is another limitation, as atypical cases or cases treated successfully are more likely to be published.

In summary, data are currently too limited for definitive conclusions to be drawn. Nevertheless, the data obtained

suggest that PA appears from 50 years of age and is slightly more frequent in men. PE is generally bilateral and involves less than a third of the hemithorax. PF is usually serous, may be a transudate or exudate, is generally lymphocyte-rich and does not have a specific pattern. On suspicion of a PA in a unilateral or exudative PE, a pleural biopsy may help establish diagnosis. Therapies for PE are rarely effective. Further studies are necessary to determine whether there are definitive therapeutic options for PE in these patients.

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

References

1. Lachmann HJ, Hawkins PN. Systemic amyloidosis. Curr Opin Pharmacol 2006;6:214-20.
2. Wechalekar AD, Gillmore JD, Hawkins PN. Systemic amyloidosis. Lancet 2016;387:2641-54.
3. Sipe JD, Benson MD, Buxbaum JN, Ikeda S, Merlini G, Saraiva MJ, *et al*. Nomenclature 2014: Amyloid fibril proteins and clinical classification of the amyloidosis. Amyloid 2014;21:221-4.
4. Kyle RA, Linos A, Beard CM, Linke RP, Gertz MA, O'Fallon WM, *et al*. Incidence and natural history of primary systemic amyloidosis in Olmsted County, Minnesota, 1950 through 1989. Blood 1992;79:1817-22.
5. Berk JL. Pleural effusions in systemic amyloidosis. Curr Opin Pulm Med 2005;11:324-8.
6. Smith RR, Hutchins GM, Moore GW, Humphrey RL. Type and distribution of pulmonary parenchymal and vascular amyloid. Correlation with cardiac amyloid. Am J Med 1979;66:96-104.
7. Moher D, Liberati A, Tetzlaff J, Altman DG, PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: The PRISMA statement. BMJ 2009;339:b2535.
8. Bontemps F, Tillie-Leblond I, Coppin MC, Frehart P, Wallaert B, Ramon P, *et al*. Pleural amyloidosis: Thoracoscopic aspects. Eur Respir J 1995;8:1025-7.
9. Astoul P, Cheikh R, Cabanot C, Vialette JP, Vestri R, Boutin C. Pleural amyloidosis: Thoracoscopic diagnosis and physiopathological approach. Rev Mal Respir 1992;9:629-31.
10. Patil PD, Cua YM, Farver C, Perez RL, Mehta AC, Panchabhai TS. A 54-year-old man with anasarca, dyspnea, and recurrent bilateral pleural effusions. Chest 2017;152:e39-44.
11. Jepson EM, Rose FC, Tonkin RD. Thoracic actinomycosis. Br Med J 1958;1:1025-7.
12. Whayne TF Jr., Burkholder PM, Becker EL. Primary amyloidosis. J Chronic Dis 1966;19:1145-56.
13. Myers GS, Castleman B. Case records of the Massachusetts general hospital. Weekly clinicopathological exercises. Case 23-1967 – Eighty six year-old man with dyspnea and generalized edema. N Engl J Med 1967;276:1252-9.
14. Clinicopathologic conference. Pleural effusion, dyspnea, and progressive liver enlargement. N Y State J Med 1968;68:1404-12.
15. Coon J, Resnekov L, Lichtig C, Straus F 2nd. Clinical-pathologic conference. Am Heart J 1974;88:496-502.
16. Clinical conference: Intractable heart failure. N Y State J Med 1975;75:1235-46.
17. Wilson SR, Sanders DE, Delarue NC. Intrathoracic manifestations of amyloid disease. Radiology 1976;120:283-9.
18. Kanarek DJ, Mark EJ. Case records of the Massachusetts general hospital. Weekly clinicopathological exercises. Case 48-1977 – Dyspnea associated with pleural thickening and interstitial pulmonary disease. N Engl J Med 1977;297:1221-8.
19. Cardiac failure and proteinuria. Am J Med 1977;63:273-8.
20. Fitzer PM. Isolated nodular pulmonary amyloidosis. Va Med 1978;105:53-5.
21. Baim S, Samuelson CO, Ward JR. Rheumatoid arthritis, amyloidosis, and chylous effusions. Arthritis Rheum 1979;22:182-5.
22. Fournial F, Ravoteur B, Carre JC, Carriere JC, Delsol G, Bollinelli R. Broncho-pulmonary amylosis (about two cases) (author's transl). Poumon Coeur 1979;35:97-100.
23. Simon BG, Moutsopoulos HM. Primary amyloidosis resembling sicca syndrome. Arthritis Rheum 1979;22:932-4.
24. Vilaseca J, Cuevas J, Fresno M, Tor J, Guardia J, Barcardi R. Systemic amyloidosis in cystic fibrosis. Am J Dis Child 1981;135:667.
25. Hiasa Y, Konishi N, Kitahori Y, Yuasa T, Fujita T, Hirao Y, *et al*. Secondary systemic amyloidosis with Hodgkin's disease. Acta Pathol Jpn 1983;33:1069-77.
26. Hiasa Y, Kitahori Y, Konishi N, Shimoyama T, Sakaguchi Y, Seki A, *et al*. Primary systemic amyloidosis with severe cardiac amyloidosis. Acta Pathol Jpn 1985;35:905-14.
27. Eisenberg R, Sharma OP. Primary pulmonary amyloidosis. An unusual case with 14 years' survival. Chest 1986;89:889-91.
28. Mitnick HJ, Tunick P, Boyd A, Smiles SA, Choy R. Subcutaneous thoracentesis utilizing an Ommaya reservoir in amyloid cardiomyopathy. JAMA 1986;255:1170-1.
29. Graham DR, Ahmad D. Amyloidosis with pleural involvement. Eur Respir J 1988;1:571-2.
30. Knapp MJ, Roggli VL, Kim J, Moore JO, Shelburne JD. Pleural amyloidosis. Arch Pathol Lab Med 1988;112:57-60.
31. Lindemalm C, Biberfeld P, Christensson B, Eriksson C, Haverling M, Tornling G, *et al*. Bilateral pleural effusions due to amyloidosis in a case of Waldenström's macroglobulinemia. Haematologica 1988;73:407-9.
32. Rainfray M, Meyrier A, Valeyre D, Tazi A, Battesti JP. Renal amyloidosis complicating sarcoidosis. Thorax 1988;43:422-3.
33. Kavuru MS, Adamo JP, Ahmad M, Mehta AC, Gephardt GN. Amyloidosis and pleural disease. Chest 1990;98:20-3.
34. Romero Candeira S, Martín Serrano C, Hernandez Blasco L. Amyloidosis and pleural disease. Chest 1991;100:292-3.
35. Salem DN, Southern JF. Case records of the Massachusetts general hospital. Weekly clinicopathological exercises. Case 44-1990 – A 71-year-old woman with biventricular heart failure, a rash, and Hilar lymphadenopathy. N Engl J Med 1990;323:1261-70.
36. Ballester Belda JE, Godoy Rocati DV, García Deltoro M, Calvo Catalá J, San Martín O, Botella Estrada R. Dyspnea as the first clinical manifestation of amyloidosis. An Med Interna 1992;9:186-8.
37. Smith FB, Brown RB, Maguire G, Oliver J. Localized pleural microdeposition of type A amyloid in a patient with rheumatoid pleuritis. Histologic distinction from pleural involvement in systemic amyloidosis. Am J Clin Pathol 1993;99:261-4.
38. Spyridopoulos I, Helber U, Voelker W, Huppert PE, Gärtner HV, Saal JG, *et al*. Primary systemic amyloidosis leading to advanced renal and cardiac involvement in a 30-year old man. Clin Investig 1994;72:462-5.
39. Berger P, Vernejoux JM, Duclos F, Villanueva P, Taytard A. Presumed transudative pleural effusion? Rev Mal Respir 1995;12:377-9.
40. Mathews M, Seth H, Guzman M, Desai S, Sein V, Shinar B. Persistent pleural effusions in systemic AL amyloidosis. Am J Respir Crit Care Med 2013;187:A6132.
41. Quinquenel ML, Le Coz A, Desrues B, Caulet-Maugendre S, Lena H, Belleguic C, *et al*. Amylose pleurale. A propos d'un cas et revue de la littérature. Rev Pneumol Clin 1996;52:39-41.

42. Arriero JM, Esparcia A, Signes-Costa J. Recurrent pleural effusion as a manifestation of primary amyloidosis. Arch Bronconeumol 1999;35:464.
43. Ikeda S, Takabayashi Y, Maejima Y, Tachibana N, Ehara T, Nezu A, *et al.* Nodular lung disease with five year survival and unilateral pleural effusion in AL amyloidosis. Amyloid 1999;6:292-6.
44. Iturbe Hernández T, Fuertes Palacio MA, Soler Mantilla H, Gutiérrez Martín M. Derrame pleural bilateral asociado a amiloidosis en un mieloma múltiple. Rev Oncología 2000;2:168-9.
45. Maeno T, Sando Y, Tsukagoshi M, Suga T, Endo M, Seki R, *et al.* Pleural amyloidosis in a patient with intractable pleural effusion and multiple myeloma. Respirology 2000;5:79-80.
46. Cable C, Hodges J, Tak T. 71-year-old male with progressive dyspnoea and peripheral oedema: A case of cardiac amyloidosis. Neth Heart J 2001;9:182-4.
47. Berk JL, Keane J, Seldin DC, Sanchorawala V, Koyama J, Dember LM, *et al.* Persistent pleural effusions in primary systemic amyloidosis: Etiology and prognosis. Chest 2003;124:969-77.
48. Fujimoto N, Masuoka H, Kosaka H, Ota S, Ito M, Nakano T. Primary amyloidosis with pulmonary involvement which presented exudative pleural effusion and high fever. Intern Med 2003;42:756-60.
49. Granel B, Serratrice J, Disdier P, Weiller PJ, Astoul P. Systemic amyloidosis with pleural involvement. Am J Med 2003;115:742-3.
50. Hofer JF, Wimmer G. Severe heart failure from light chain cardiomyopathy (cardiac amyloidosis). Z Kardiol 2003;92:90-5.
51. Leleu O, Clarot C, Renaud H, Brahimi M, Lelarge C, Makdassi R. Amyloidosis and pleural calcification. Rev Mal Respir 2003;20:618-21.
52. Daniil Z, Zakynthinos E, Papageorgiou E, Loannou M, Kostikas K, Gourgoulianis K. Amyloid cardiomyopathy presenting as persistent symptomatic pleural effusions. Respir Med Extra 2005;1:79-80.
53. Dember LM, Shepard JA, Nesta F, Stone JR. Case records of the Massachusetts General hospital. Case 15-2005. An 80-year-old man with shortness of breath, edema, and proteinuria. N Engl J Med 2005;352:2111-9.
54. Diaz-Guzman E, Culver DA, Stoller JK. Transudative chylothorax: Report of two cases and review of the literature. Lung 2005;183:169-75.
55. Suzuki M, Betsuyaku T, Kojima T, Saito H, Nishiura Y, Fukasawa Y, *et al.* Pleural involvement of dialysis-related amyloidosis. Intern Med 2005;44:628-31.
56. Cabeza Letrán L, Gallego Puerto P, Anglada Pintado JC, Esquitino del Río B. Pleural effusion in systemic primary amyloidosis. An Med Interna 2006;23:96-7.
57. McGowan N. What's wrong with this patient? Primary systemic amyloidosis. RN 2006;69:37-40.
58. Roubille F, Billotet C, Roubille C. Original case report of amyloidosis with pleural involvement: The role of echocardiography in the diagnosis. Rev Med Interne 2006;27:794-6.
59. Hoyer RJ, Leung N, Witzig TE, Lacy MQ. Treatment of diuretic refractory pleural effusions with bevacizumab in four patients with primary systemic amyloidosis. Am J Hematol 2007;82:409-13.
60. Pérez Rodríguez MT, Martínez Vázquez C, González Villarroel P, Sopeña Pérez-Argüelles B, Fernández Villar A. Transudate type pleural effusion as expression of pleural involvement due to amyloidosis. Rev Clin Esp 2007;207:534-5.
61. Jeannin G, Marson H, Merle P, Janicot H, Greil A, Caillaud D. An unusual cause of chylothorax: Primary amyloidosis. Rev Mal Respir 2008;25:601-4.
62. Briggs JH, Singleton WG, Burke MM, Hart LA, Parker RJ. Amyloidosis presenting as bilateral transudative pleural effusions with normal cardiac investigations: A case report. Cases J 2009;2:6963.
63. Schwarz D, Jue C, Sikov W. Primary systemic amyloidosis and persistent pleural effusions. Amyloid 2009;16:239-42.
64. Silvestre OM, Ribeiro HB, Paula LJ, Macêdo SR, Castelli JB. Case 5: 50-year-old woman with restrictive cardiomyopathy, renal failure and proteinuria. Arq Bras Cardiol 2009;93:569-77.
65. Aichaouia C, Ben Meftah MR, M'hamdi S, Laabidi J, Moatamri Z, Haddaoui A, *et al.* Pleural amyloidosis attesting to generalised amyloidosis. Rev Pneumol Clin 2010;66:204-8.
66. Araoka T, Takeoka H, Nishioka K, Ikeda M, Kondo M, Hoshina A, *et al.* Successful management of refractory pleural effusion due to systemic immunoglobulin light chain amyloidosis by vincristine adriamycin dexamethasone chemotherapy: A case report. J Med Case Rep 2010;4:322.
67. Bae SH, Hwang JY, Kim WJ, Yoon HH, Kim JM, Nam YH, *et al.* A case of cardiac amyloidosis with diuretic-refractory pleural effusions treated with bevacizumab. Korean Circ J 2010;40:671-6.
68. Horton MR. Anasarca and chylous effusions: An unusual presentation of systemic amyloidosis. Am J Case Rep 2010;11:191-4.
69. Roden AC, Aubry MC, Zhang K, Brady JO, Levin D, Dogan A, *et al.* Nodular senile pulmonary amyloidosis: A unique case confirmed by immunohistochemistry, mass spectrometry, and genetic study. Hum Pathol 2010;41:1040-5.
70. El Boukhrissi F, Balouch L, Hachimi MA, Hommadi A, Idrissi MM, Bamou Y. Bilateral pleurisy revealing a myelome with free light chains complicated with an osseous amylose. Ann Biol Clin (Paris) 2011;69:593-6.
71. Erickson B, Dhaliwal G, Henderson MC, Amsterdam E, Rencic J. Effusive reasoning. J Gen Intern Med 2011;26:1204-8.
72. Mansalis KA, Klein DA, Demartini SD, Powers JF, Danielson DS. Pleural findings in a patient with persistent pulmonary effusions from systemic amyloidosis. Amyloid 2011;18:29-31.
73. Rafii R, Leslie K, Heo J, Chan A. A 71-year-old woman with an unusual cause for pleural effusions. Chest 2011;139:1237-41.
74. Agarwal A, Singla S, Bansal M, Nair B. Bilateral pleural effusions due to pulmonary amyloidosis as the presenting manifestation of multiple myeloma. Mediterr J Hematol Infect Dis 2012;4:e2012010.
75. Chu H, Zhao L, Zhang Z, Gui T, Yi X, Sun X. Clinical characteristics of amyloidosis with isolated respiratory system involvement: A review of 13 cases. Ann Thorac Med 2012;7:243-9.
76. Shimizu Y, Endou K, Hashizume Y, Kawata T, Horie T, Ogura H, *et al.* Massive pleural effusion due to pleural AA amyloidosis. Am J Respir Crit Care Med 2012;186:e19-20.
77. Franco-Palacios D, Tama M, Samaddar S, Yang J. Retroperitoneal amyloidosis as the presenting manifestation of Waldenstrom's macroglobulinaemia. BMJ Case Rep 2013;2013:bcr2013009329.
78. Harvey-Taylor J, Zhang Y, Kuderer V, Cooke DT. Diagnosis of systemic amyloidosis and amyloidosis mediated cardiomyopathy by VATS pleural biopsy for chronic pleural effusion. J Thorac Dis 2013;5:E112-4.
79. Jamieson DB, Bose S, Feller-Kopman D, Imad M, Yarmus L. A therapeutic thoracoscopy. Ann Am Thorac Soc 2013;10:163-5.
80. Karim S, Chang YS. An unusual cause of pleural effusion. N Z Med J 2013;126:79-81.
81. George S, Ravindran M, Anandan PT, Kiran VN. Primary systemic amyloidosis: A rare cause for pleural effusion. Respir Med Case Rep 2014;13:39-42.
82. Ishiguro T, Takayanagi N, Katoh N, Shimizu Y, Hoshi T, Yanagisawa T, *et al.* Waldenström's macroglobulinemia accompanying systemic amyloidosis: The usefulness of endobronchial ultrasound-guided transbronchial needle aspiration for detecting amyloid deposits. Intern Med 2014;53:2789-93.
83. Johnston EL, Wilkinson M, Knisely AS. Vasotropic light-chain amyloidosis and ischaemic cholangiopathy. BMJ Case Rep 2015;2015:bcr2015210883.
84. Tada L, Anjum H, Linville WK, Surani S. Recurrent pleural effusions occurring in association with primary pulmonary amyloidosis. Case Rep Pulmonol 2015;2015:421201.

85. Roh EK, Ali M, Lu MT, Bradshaw SH. Case 2-2016. An 84-year-old woman with chest pain, dyspnea, and a rash. N Engl J Med 2016;374:264-74.
86. Chen HH, Kilic AI, Picken M, Pambuccian SE, Wojcik EM. Amyloid in endobronchial ultrasound-guided transbronchial needle aspiration cytology. Diagn Cytopathol 2017;45:436-40.
87. Coolbear F, Bilawich AM, Tongson J, Adamo J, Churg A. Pleural amyloidosis imitating pleural malignancy. Respir Med Case Rep 2017;20:195-7.
88. Dias C, Tavares I, Magalhães A, Melo N. Pleural effusion in AA amyloidosis – A rare involvement of a rare disease. Rev Port Pneumol (2006) 2017;23:234-6.
89. Chen P, Wang Z, Liu H, Liu D, Gong Z, Qi J, *et al*. Clinical characteristics and diagnosis of a rare case of systemic AL amyloidosis: A descriptive study. Oncotarget 2018;9:24283-90.
90. Kanno Y, Furuya N, Okamoto M, Noguchi A, Inoue T, Mineshita M. Narrow-band imaging thoracoscopy in pleural amyloidosis. Respirol Case Rep 2018;6:e00305.
91. Manur R, Lamzabi I. Amyloidosis diagnosed in cytology specimen of pleural effusion: A case report. Diagn Cytopathol 2018;46:522-4.
92. Xiong J, Ren Y, Li H, Fu B, Wu R. First case of pleural amyloidosis in systemic erythematosus: Report and literature review. Z Rheumatol 2018;77:841-3.
93. Dai Y, Liu C, Chen J, Zeng Q, Duan C. Pleural amyloidosis with recurrent pleural effusion and pulmonary embolism: A case report. Medicine (Baltimore) 2019;98:e14151.
94. Sucu S, Bozdag Z, Agar B, Ozcan HC, Komurcu O, Balat O. Multiple myeloma-associated amyloidosis mimicking peritoneal carcinomatosis: an unusual case report. J Clin Obst Gyn 2019;29:116-9.
95. Binder C, Duca F, Binder T, Rettl R, Dachs TM, Seirer B, *et al*. Prognostic implications of pericardial and pleural effusion in patients with cardiac amyloidosis. Clin Res Cardiol 2021;110:532-43.
96. Lachira-Yparraguirre L, Al-kassab-Córdova A, Quispe-Silvestre E, Enríquez-Vera D. Amiloidosis cardiaca secundaria a macroglobulinemia de Waldenström. Rev Cubana Hematol Inmunol Hemoter 2020;36:e1202.
97. Noda H, Nitta M, Taguchi Y, Matsumoto K, Sugano T, Ishigami T, *et al*. Importance of pleural findings in patients with amyloid cardiomyopathy complicated with refractory pleural effusion. J Cardiol Cases 2020;21:205-8.
98. Shibata R, Ozaki T, Tada K, Aoyama T, Watanabe M, Himuro N, *et al*. Secondary renal amyloidosis associated with asbestos-related pleuropulmonary diseases. CEN Case Rep 2020;9:385-91.
99. Srinivasan A, Chowdhuri SR, Grosu HB. Pleural amyloid as a cause of symptomatic effusion. J Bronchology Interv Pulmonol 2020;27:e45-7.
100. Chan R, Carpentier S. Gastric amyloidosis presenting as acute upper gastrointestinal bleeding: A case report. BMC Gastroenterol 2021;21:300.
101. Munagala R, Mishra P, Lodh A, Shukla D, Bhatt A, Taskar V, *et al*. Mystery in the mediastinum: Rare case of indolent primary thoracic amyloids. Lung India 2021;38:374-6.
102. Saad W, Moussa M, Saad F, Dbouk S, Bazzi N. Cardiac amyloidosis with overt multiple myeloma presenting with pulmonary effusion: Case report. J Surg Case Rep 2021;2021:rjab279.
103. Light RW, Macgregor MI, Luchsinger PC, Ball WC Jr. Pleural effusions: The diagnostic separation of transudates and exudates. Ann Intern Med 1972;77:507-13.
104. Ferreiro L, Porcel JM, Valdés L. Diagnóstico y manejo de los trasudados pleurales. Arch Bronconeumol 2017;53:629-36.