



Small Cell Lymphocytic Lymphoma: An Unexpected Etiology of Pleural Effusion

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Abstract

The differential diagnosis of pleural effusion is extensive. Pleural fluid characteristics are helpful in classifying, as transudate or exudate, being this determinant to achieve an accurate diagnosis.

The authors present a clinical report of a 74-year-old man with reduced left ventricular ejection fraction heart failure, of ischemic etiology, and multiple cardiovascular risk factors, who develops a pleural effusion. In his medical history it is important to denote a recent diagnosis of colon adenocarcinoma, without evidence of metastatic disease, submitted to hemicolectomy. Four months after this diagnosis, he was admitted in the Emergency Department with dyspnea, type 1 respiratory failure and de novo pleural effusion. The most probable etiologies of pleural effusion were excluded, including heart failure and a metastatic disease. Ultimately, it was reported a difficult (or not so) and unexpected etiology for the pleural effusion, in a patient with multimorbidity and multiple confounders.

It is crucial to see beyond the obvious. A real-life challenge for Internal Medicine.

Keywords: heart failure, pleural effusion, percutaneous mitral edge-to-edge repair, small cell lymphocytic lymphoma, colon adenocarcinoma.

Introduction

The amount of pleural fluid is dependent on the balance between the movement of pleural fluid from the parietal pleura to the pleural space and subsequent resorption by lymphatic vessels of the parietal pleura. The dysregulation of this homeostasis is responsible for the development of pleural effusion^[1].

There are five main pathophysiological processes involved: increased fluid production due to increased hydrostatic pressure or decreased oncotic pressure in the presence of adequate vascular permeability (transudate), increased fluid production with increased vascular permeability (exudate), reduced fluid clearance by the lymphatic system (exudate), infectious causes (empyema) or existence of an active bleeding (hemothorax)^[1].

The differential diagnosis of pleural effusion is extensive. The characteristics of the pleural fluid are helpful in classifying it as transudate or exudate. Congestive heart failure is the most frequent cause of transudate, accounting for more than 90% of cases. The leading causes of exudative effusions are pneumonia and cancer^[2,3]. Primary tumors that most frequently develop malignant pleural effusions are lung, breast cancer and lymphoma, accounting for 75% of all cases^[2].

Thus, pleural effusion has a wide array of etiologies and the most likely one is not always the precise one. This clinical case report aims to highlight the importance of a holistic, systematic approach to the patient, even when he seems to have an obvious cause for his symptoms.

Case Report

We describe a 74-year-old man with reduced left ventricular ejection fraction (LVEF) heart failure (HF) of ischemic etiology (New York Heart Association - NYHA - class II), with various cardiovascular risk factors: hypertension, obesity (body mass index of 30.1Kg/m²) and previous smoking (32 units pack per year).

The patient had a long course three-vessel coronary heart disease, since 1996. After coronary artery bypass graft surgery and multivessel angioplasty, cardiac recatheterization was performed in 2008 showing multivessel obstructive disease and mild inferolateral ischemia with no indication for further revascularization procedures.

In April 2021 the patient suffered a Killip III non-ST segment elevation myocardial infarction and was successfully submitted to cardiac catheterization and left main coronary artery and circumflex artery angioplasty with a drug-eluting stent. A severe dynamic mitral regurgitation with multiple recurrent episodes of acute pulmonary edema made him a suitable candidate for percutaneous mitral edge-to-edge repair.

During that hospitalization, an iron deficiency anemia due to hematochezia was reported, with digestive tract endoscopy

revealing an ulcerated infiltrative lesion of the hepatic angle. The anathomopathological study was compatible with a low-grade adenocarcinoma and there was no evidence of metastatic disease (in computed tomography (CT) scan). After weighing the risk-benefits for the patient, a right hemicolectomy was done, in May 2021. At discharge, the patient was eupneic on room air without signs of pulmonary congestion or peripheral edema and was afterwards referred to the Oncology outpatient clinic, where he maintained follow-up.

Stable until August 2021, he was then admitted in the Emergency Department (ED) with dyspnea for mild exertion, orthopnea and paroxysmal nocturnal dyspnea with a 10-day evolution. At admission, he was afebrile, hypotensive (94/65mmHg), with regular rhythm and rate (80 beats per minute), polypneic (26 cycles per minute), with peripheral oxygen saturation (SpO₂) of 88% in room air (**Table 1**). On physical examination, he had bilateral inspiratory rales and wheezing on auscultation and bilateral, symmetric lower limb edema. Blood tests showed an acute kidney injury and type 1 respiratory failure, with no elevation of inflammatory parameters or markers of acute myocardial infarction (**Table 1**). A chest X-ray showed a de novo right pleural effusion (**Figure 1**).

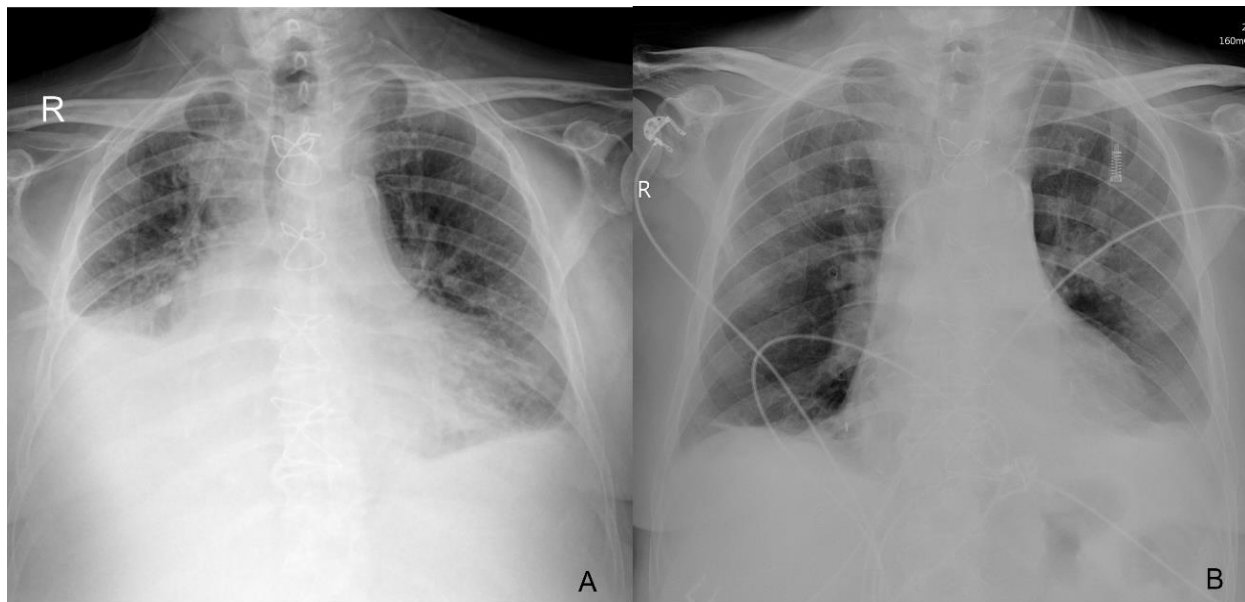


Figure 1: A) Chest x-ray in august 2021. B) Chest x-ray in april 2021.

At this time, acute decompensated chronic heart failure seemed to be the most probable etiology for the pleural effusion. The patient started intravenous diuretic therapy and supplementary oxygen therapy and was admitted to the Heart Failure Unit (HF Unit).

In the first 24 hours of hospitalization, the patient had a clinical and blood gas worsening with progression to type 2 respiratory failure and respiratory acidemia requiring non-invasive ventilation (NIV) in bilevel mode, which was titrated according to blood gas evolution (**Table 1**).

Due to progressive clinical worsening and maintenance of pleural effusion, after high dose IV diuretic therapy, thoracentesis was performed, with a 1900 mL initial outflow of hematic pleural fluid, and a total drainage of 5700 mL, followed by blood gas improvement. NIV was withdrawn on the 3rd day and supplementary oxygen therapy on the 12th day after admission.

Biochemistry of pleural fluid revealed an exudate according to Light's criteria; cytological examination showed a predominance of lymphocytes (42%), suggesting neoplastic etiology (in a patient with previous history of colon

adenocarcinoma). Pleural fluid immunophenotyping was compatible with Small Cell Lymphocytic Lymphoma (SCLL), and peripheral blood immunophenotyping corroborated this hypothesis (**Table 1**).

After the involvement of Hematology and considering patient's age, current symptoms (pleural effusion requiring supplemental oxygen) and extranodal involvement, the patient was started on chlorambucil 2 mg per day.

During hospitalization in the HF Unit, reduced Ejection Fraction HF (HFrEF) prognosis-modifying therapy was optimized.

On the 17th day of hospitalization and after clinical stabilization, the patient underwent percutaneous mitral edge-to-edge repair, which was uneventful. He was discharged after 24 hours, clinically stable, in NYHA class II, analytically improved (**Table 1**) and referred to the HF Outpatient Clinic. Regarding prognostic-modifying therapy, at the time of discharge the patient was on sacubitril-valsartan 24/26mg twice daily, bisoprolol 2.5mg, spironolactone 25mg and dapagliflozin 10mg. The patient maintained chlorambucil 2 mg/day as well.

Table 1: Complementary diagnostic tests during hospitalization

Complementary diagnostic test	Admission (18/08/2021)	1 st day of Hospitalization (20/08/2021)	Discharge date (07/08/2021)
Blood tests results			
Hemoglobin	10,1g/dL	10,6g/dL	8,3g/dL
Leucocytes	6,1 x 10 ⁹ /L	6,2 x 10 ⁹ /L	7,1 x 10 ⁹ /L
Neutrophils	51,4%	73,9%	58%
Lymphocytes	44,1%	23,2%	38%
C-Reactive protein	0,46mg/dL	1,29mg/dL	3,31mg/dL
Procalcitonin	0,04ng/mL	-	-
Platelets	180 x 10 ⁹ /L	176 x 10 ⁹ /L	251 x 10 ⁹ /L
Sedimentation rate	-	38mm/h	-
Lactate dehydrogenase	168 U/L	168 U/L	190 U/L
Serum total proteins	-	6,1g/dL	-
Ferritin	-	120ng/mL	122ng/mL
Transferrin saturation	-	24%	19%
Creatinine	1,83mg/dL	1,26mg/dL	1,40mg/dL
Urea	53mg/dl	42mg/dL	87mg/dL
Glomerular filtration rate (Chronic Kidney Disease Epidemiology Collaboration equation)	36 mL/min/1,73m ²	55mL/min/1,73m ²	49mL/min/1,73m ²
Aspartate transaminase	13UI/L	21UI/L	23UI/L
Alanine aminotransferase	15UI/L	15UI/L	36UI/L
Gamma-glutamyl transferase	-	27UI/L	-
Alkaline phosphatase	-	54UI/L	-
Total bilirubin	-	0,94mg/dL	-
Glycaemia	-	123mg/dL	-
Glycated haemoglobin	5,2%	-	-
NTproBNP	1539pg/mL	4727pg/mL	648pg/mL
Troponin I	44ng/L	42ng/L	-
Thyroid stimulating hormone	-	0,488uUI/mL	-
Free T4	-	23,5pmol/L	-
Imunophenotyping of peripheral blood	-	4,6% of monoclonal B lymphoid cells with phenotype overlapping that of pleural fluid, compatible with CLL/SCLL	-
Arterial blood gases	Under FiO ₂ of 28%	Under NIV, in BPAP mode with IPAP 18, EPAP 8, RR18, O2 a 15L/min	Under FiO ₂ of 21%
pH	7,43	7,299	7,413
PaCO ₂	51,1mmHg	75,4mmHg	47,5mmHg
PaO ₂	68,6mmHg	68,4mmHg	85,4mmHg
HCO ₃	32mmol/L	31,7mmol/L	30,3mmol/L
Lactic acid	1,0mmol/L	0,8mmol/L	0,80mmol/L
Sodium	146mmol/L	143mmol/L	136 mmol/L
Potassium	3,74mmol/L	4,34mmol/L	4,41 mmol/L
Transcription-polymerase chain reaction for SARS-CoV-2	Negative	-	-
Analysis of pleural effusion			
Aspect	-	Hematic	-
Density	-	1021	-
pH	-	7,413	-
Glycose	-	137mg/dL	-
Proteins	-	2,6g/dL	-
Lactate dehydrogenase	-	107U/L	-
Total nucleated cells	-	856 cells/uL	-
Neutrophils	-	18%	-
Lymphocytes	-	42%	-
Monocytes/macrophages	-	40%	-
Adenosine deaminase	-	2,5 U/L	-
Observations	-	Some mesothelial cells with atypical morphology – activated cells? Metastases?	-
Immunophenotyping of pleural fluid	-	21,3% of monoclonal B lymphoid cells with phenotype compatible with SCLL	-

In HF outpatient clinic reassessment, one week after hospital discharge, the patient maintained NYHA class II, without signs of lung congestion or peripheral edema. Sacubitril/valsartan therapy was up-titrated to 49 / 51 milligrams twice daily. Considering the functional iron deficiency with anemia at discharge, a total of 2000 milligrams of intravenous ferric carboxymaltose was administered, in two sessions.

Currently, patient maintains follow-up in the Heart failure, Hematology, Oncology and General Surgery specialties.

Discussion

The authors present a case of a patient who has several possible etiologies for his pleural effusion.

In a patient with HFrEF and a long-term ischemic heart disease, not eligible for revascularization, and severe functional mitral regurgitation, already proposed for percutaneous mitral edge-to-edge repair, a new ischemic event was one of the most probable etiologies of acute decompensated HF with pleural effusion. However, serial evaluation of acute myocardial infarction markers was negative. A transient ischemia could also be the trigger for severe mitral valve regurgitation and acute decompensated HF and, in this case, acute myocardial infarction markers would expectably be negative.

Also, bearing in mind the recent diagnosis of colon adenocarcinoma and analyses of macroscopic characteristics of pleural fluid and cytochemical examination, both suggested the hypothesis of a neoplastic etiology. An unexpected diagnosis of Chronic Lymphocytic Leukemia (CLL)/SCLL was obtained from the pleural fluid and peripheral blood immunophenotyping.

CLL is the most common Leukemia in the Western World, with an incidence of 4,2 per 100,000/year, and its incidence increases with age [4]. The average age at diagnosis is 72 years old and it mainly affects males [4].

In the 2017 World Health Organization (WHO) Classification, SCLL and CLL are considered a single entity since cells have the same phenotype. However, while CLL is a hematologic malignancy, in SCLL there are other factors to be considered. When peripheral blood B-lymphocyte count is less than $5 \times 10^9/L$ and co-exists with lymphadenopathy and/or splenomegaly (diagnosed either on physical examination or by imaging methods) diagnosis of SCLL should be considered instead [4,5].

SCLL is a lymphoproliferative disorder that has an indolent course [4]. After the diagnosis, patient survival can be up to 12 years [6]. In the presented clinical case, the diagnosis was made after the diagnosis of colon adenocarcinoma, however, SCLL probably already existed, being the colon adenocarcinoma or the immunosuppression induced by chemotherapy possible triggers for the outbreak of the lymphoproliferative disease.

The relationship between CLL/SCLL and colon adenocarcinoma does not seem to be a coincidence. Patients diagnosed with one neoplasm are at an increased risk for developing a second one (solid organ or hematologic) [7]. On the other hand, the appearance of another malignancy in a patient with CLL/SCLL is related to the patient's survival, meaning that, the longer the patient survival, the greater the risk of developing another neoplasm [7].

L. Falchi *et al* [6] reported, when compared to the general population, that survivors of CLL had a significant increase in the risk of another malignancy, 36% had the diagnosis of another neoplasm.

The factors that intervene in this relationship are not known, but there are several hypothesis including genetic predisposition, existence of likely shared risk factors, immune dysregulation induced by CLL/SCLL or chemotherapy itself, which may be responsible for this increased risk.

There is currently no available data in the published literature that documents pleural effusion as the predominant clinical feature in the diagnosis of SCLL and further studies are needed to correctly establish a relationship between the two clinical entities and the risk factors that may be involved.

Conclusions

This clinical report constitutes a paradigm for Internal Medicine. Aging potentiates multimorbidity, which often behaves as

confounders, making diagnosis and treatment a challenge. The case report illustrates the complexity of Internal Medicine nowadays.

Ethics approval and consent to participate

“Not applicable”.

List of abbreviations

CLL: Chronic Lymphocytic Leukemia
CT: Computed tomography
ED: Emergency department
HF: Heart failure
HFrEF: Heart failure with Reduced Ejection Fraction
LVEF: Left ventricular ejection fraction
NIV: Non-invasive ventilation
NYHA: New York Heart Association
SCLL: Small Cell Lymphocytic Lymphoma
SpO2: Peripheral oxygen saturation
WHO: World Health Organization

Data Availability

“Not applicable”.

Conflicts of Interest

“The author(s) declare(s) that there is no conflict of interest regarding the publication of this paper.”

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Authors' contributions

FS, research design, data collection drafting of the paper and spelling revision.
SR, CP, PM, JT, MC, PS, research design, data collection.
JD, IA, CF, intellectual content revision.
All authors read and approved the final manuscript.

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