CASE REPORT

Case Report: A rare case of a vanishing unilateral effusion

[version 1; peer review: 1 approved with reservations]

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Abstract

Pleural effusions rarely spontaneously resolve, and we document an instance where this phenomenon occurred. Here, we report a case of a 95-year old female who presented with a unilateral pleural effusion, diagnosed as secondary to a haematological malignancy [diffuse large B-cell lymphoma (DLBCL)] which resolved spontaneously. This is the first case to describe spontaneous remission in a primary cavitory DLBCL complicated by pleural effusion.

Keywords

pleura, lymphoma, pleural effusion, malignant, neoplasm, remission, case report

Peer review discontinued

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Approval Status ?

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1. Paul Stockhammer , Yale University, New Haven, USA	
Any reports and responses or comments on the article can be found at the end of the article.	

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Introduction

Pleural effusions are frequently encountered within the respiratory outpatient setting. There are a wide range of causes and potential interventions to be offered in order to diagnose and treat effusions. Pleural effusions rarely spontaneously resolve, and here we report an interesting case where this rare phenomenon occurred.

Patient information

A 95-year old Caucasian female was seen in July 2018 in a community respiratory clinic with a 4-month history of increasing breathlessness and a widespread vasculitic-looking rash. She had a background of high blood pressure and stable non-vasculitic chronic kidney disease. She lived alone and was fully independent with all activities of daily living.

Clinical findings

The clinical features on examination were in keeping with a left sided pleural effusion.

Timeline

The patient was followed over the course of 6 months in 2018.

Diagnostic assessment

She had a chest X-ray (Figure 1a) which showed a moderate left sided effusion, and subsequent computed tomography (CT) (Figure 1b) confirmed the presence of an effusion, along

with mediastinal lymphadenopathy. An echocardiogram showed normal left ventricular function with moderate mitral stenosis and mild mitral regurgitation. A positron emission tomography (PET) CT scan did not suggest any size significant or fluorodeoxyglucose (FDG) avid hilar or mediastinal lymphadenopathy.

Pleural aspiration was performed with 700 millilitres of yellow serous fluid obtained (exudative, protein - 47g/l, lactate dehydrogenase (LDH) - 3072U/l, negative microbiology culture). Other investigations demonstrated a negative vasculitis screen, serum LDH of 392U/l (<250U/l), and a small paraprotein was detected on immunofixation.

Fluid cytology revealed a diffuse population of intermediate to large sized lymphoid cells containing moderate amphophilic cytoplasm and round nucleus with fine chromatin and conspicuous nucleoli, some of them with plasmacytoid appearance. The lesional cells were of lymphoid B-cell lineage as evidenced by strong, diffuse expression of CD45, CD20 and PAX-5. A proportion of these cells co-expressed BCL-6 (90% of cells), BCL-2 (90%) and MUM1 (>80%), but not CD10, CD5, CD56, CD138, TdT, CD30, CD38, Cyclin-D1 or CD23. There was c-myc expression in approximately 80%. The proliferation fraction estimated by Ki-67 marker was high at approximately 80%. TTF-1 and MNF116 were negative. EBER (Epstein Barr virus-encoded small RNA) *in situ* hybridization

Panel 1: Chest radiograph - Left sided pleural effusion (A)

Panel 2: CT chest showing (B) Left sided pleural effusion and (C) resolution

Figure 1. Clinical imaging of the patient (A) Chest radiograph showing left sided pleural effusion (B) computed tomography (CT) chest showing left sided pleural effusion (C) CT chest showing resolution of left sided pleural effusion.

for Epstein-Barr virus (EBV) was negative. The appearances were consistent with a high-grade, non-Hodgkin B-cell lymphoma, in keeping with a diffuse large B-cell lymphoma, not otherwise specified (DLBCL NOS). The immunohistochemical appearances were those of a non-germinal centre B-cell-like (non-GCB) subgroup.

Therapeutic intervention, follow up and outcomes

While awaiting treatment planning, repeat CT showed improvement in the effusion with resolution 6 months later; without any intervention (Figure 1c). Two years on, the patient remains symptom free, and in apparent remission.

Discussion

Primary effusion lymphoma (PEL) is a rare subtype of diffuse large B-cell lymphoma (DLBCL) and is universally associated with human herpes virus-8 (HHV-8) that involves body cavities and causes serous effusions without detectable masses or lymphadenopathy¹⁻⁴. It also occurs in immunocompromised patients infected with human immunodeficiency virus (HIV) and Epstein-Barr virus (EBV)^{2,4,5}. On the other hand, many cases of DLBCL with lymphomatous effusions on serosal surfaces, and no detectable mass lesion like PEL, have been reported. These cases were not regarded as cases of PEL, but proposed to represent a new entity, 'PEL-like lymphoma (PEL-LL)'⁶. A single-centre evaluation of 185 consecutive patients with DLBCL presenting with pleural effusions confer an independent predictor of poor survival in Cox regression modelling (hazard ratio 1.9)⁷.

The frequency of spontaneous regression of cancer has been estimated to be about 1 case per 100,000 patients, and approximately 20 cases are reported each year⁸. Hypernephroma, melanoma, neuroblastoma, leukaemia, and non-Hodgkin lymphoma are the most commonly reported cancers exhibiting spontaneous regression.

In the case we present, there was spontaneous regression of the effusion, however, the aetiology underlying the development

of spontaneous remission of malignancy remains unclear. Proposed mechanisms to explain this phenomenon include immunological, hormonal and genetic factors; concomitant infections; elimination of carcinogens; surgical trauma of the primary tumour and induction of differentiation^{9,10}.

In this case, there were no obvious precipitating factors such as infections. The apparent absence of EBER expression argues against a lymphoma associated with immune senescence. There was no evidence of acquired immunodeficiency, or prior therapeutic interventions. The Ki-67 protein is a cellular marker for proliferation; in this case it was 80%, suggesting the presence of a rapidly proliferative neoplasm¹¹. Taken into consideration previous reports associating primary cavitory DLBCL with a poor prognosis, it is noteworthy that our patient has remained in remission 2 years following her initial diagnosis, without therapeutic intervention. To our knowledge, this is the first case to describe spontaneous remission in a primary cavitory DLBCL complicated by pleural effusion.

In the case of unexplained pleural effusion, suspected to have an underlying neoplastic aetiology, clinicians should consider the possibility of haematological malignancy in the differential diagnoses, and investigate accordingly. They should also be aware that rarely, these have the potential to spontaneously resolve.

Patient perspective

Our patient was relieved to not have had to endure invasive therapies.

Consent

Written informed consent for publication of their clinical details and clinical images was obtained from the patient.

Data availability

Underlying data

All data underlying the results are available as part of the article and no additional source data are required.

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Paul Stockhammer

Yale University, New Haven, CT, USA

The authors describe an interesting case of an elderly female patient presenting with unilateral pleural effusion, who was found to have most likely primary effusion lymphoma-like lymphoma (PEL-LL), a rare entity of DLBCL confined to the serosal space. By undergoing diagnostic and therapeutic thoracentesis without any subsequent lymphoma-directed therapy, the patient went into apparent remission for at least two years. Overall, this report is of clinical relevance, given that it describes a rare subtype among the broad category of DLBCL with a rather unusual outcome. However, there are several aspects of this report that need to be addressed:

- The authors categorized the patient's lymphoma as DLBCL-NOS, but in the discussion they exclusively focus on PEL and the recently described PEL-LL. Based on immunotyping and clinical scenario, the patient should have most likely been subtyped as PEL-LL, and this should be also clearly stated in the results part. I was wondering whether the authors could provide status of HHV8, HIV and HCV in this patient (if tested, besides EBV), given that particularly HHV8 status is essential in differentiating PEL from PEL-LL. The authors should use uniform and clear nomenclature and should avoid the term primary cavitory DLBCL given that this would incorporate and not differentiate between PEL and PEL-LL.
- The abstract is misleading and should more precisely state PEL-like lymphoma instead of the broad category of DLBCL, given that most people associate the term DLBCL with systemic lymphoma, and primary effusion lymphoma represents a very distinct subtype of DLBCL.
- Can the authors comment on the vasculitic-looking rash, and if there was a presumed relation to her lymphoma?
- Can the authors include a post-thoracentesis chest X-ray, given that the therapeutic thoracentesis most likely resulted in resolution of the moderate pleural effusion. Only showing the follow-up CT scan several months later can be misleading and misinterpreted as spontaneous resorption during that time.
- By stating that the pleural effusion spontaneously resolved, the authors overstate their main findings. They identified a moderate pleural effusion, which on average contains about 680mL as per (PMID: 23632863¹). As stated by the authors, a thoracentesis with about 700mL fluid removal was performed, which should be considered as therapeutic

intervention and would thus not mean “spontaneous resolution” but rather “no re-accumulation in pleural effusion after therapeutic thoracentesis was observed”.

Interestingly, HHV8-unrelated PEL-LL with spontaneous regression of malignant cells without any additional treatment besides thoracentesis have been already reported by several groups (PMIDs: 23319997², 9850179³, 17071811⁴). Given those reports, the authors main statement of describing “the first case of spontaneous remission in primary cavitory DLBCL” as well as the articles title of “vanishing unilateral effusion” is not accurate and should be toned down. The authors should discuss those issues, and also discuss the potential mechanism of inducing cytogenic complete remission with sufficient pleural fluid drainage in patients with PEL-LL (PMID: 19075546⁵).

- The authors cited Porcel et al. with the statement that “pleural effusions associate with poor prognosis in patients with DLBCL”. However, in the cited report by Porcel et al., patients with systemic lymphomas with or without pleural effusions were analyzed and not patients with primary effusion lymphoma. As per above, PEL and PEL-LL represent completely different entities compared to systemic lymphomas, and thus the authors’ statement is misleading and should be rephrased or excluded.
- The authors should cite and discuss the review by Wu et al (PMID: 23897264⁶), who performed the so far largest literature review on HHV-8 unrelated PEL-LL cases. As indicated by Wu et al., there are some cases of patients undergoing pleural fluid drainage as the only therapy.

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Is the background of the case’s history and progression described in sufficient detail?

Partly

Are enough details provided of any physical examination and diagnostic tests, treatment given and outcomes?

Partly

Is sufficient discussion included of the importance of the findings and their relevance to future understanding of disease processes, diagnosis or treatment?

No

Is the case presented with sufficient detail to be useful for other practitioners?

Partly

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Medical Oncology - Thoracic Oncology

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

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