Case Report

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Malignant pericardial effusion complicated by cardiac tamponade under atezolizumab

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Abstract

Immune-related adverse events including cardiac toxicity are increasingly described in patients receiving immune checkpoint inhibitors. We described a malignant pericardial effusion complicated by a cardiac tamponade in an advanced non-small cell lung cancer patient who had received five infusions of atezolizumab, a PDL-1 monoclonal antibody, in combination with cabozantinib. The definitive diagnosis was quickly made by cytology examination showing typical cell abnormalities and high fluorescence cell information provided by the hematology analyzer. The administration of atezolizumab and cabozantinib was temporarily discontinued due to cardiogenic hepatic failure following cardiac tamponade. After the re-initiation of the treatment, pericardial effusion relapsed. In this patient, the analysis of the pericardial fluid led to the final diagnosis of pericardial tumor progression. This was afterwards confirmed by the finding of proliferating intrapericardial tissue by computed tomography scan and ultrasound. This report emphasizes the value of cytology analysis performed in a hematology laboratory as an accurate and immediate tool for malignancy detection in pericardial effusions.

Keywords

Pericardial effusion, non-small cell lung cancer, atezolizumab, cytology, fluorescence

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Introduction

Immune checkpoint inhibitor (ICI)-based immunotherapies have widely proven their clinical benefits in different types of malignancies and the positive efficacy/safety profile of anti-PD-1/PD-L1 complements traditional chemotherapies. However, immune-related adverse events (irAEs) are nowadays observed including potentially fatal cardiac toxicity due to excessive ICI-related autoimmune response.[1–3] Pericardial effusions with significant hemodynamic impairment in patients receiving ICIs occur in less than 1% of cases. But recent studies observed a higher incidence than expected in lung cancer patients, especially those with advanced non-small cell lung cancer (NSCLC).[1,4,5] Intriguingly, these patients had no myocardial disease, and it even led some authors to mention a more specific "pericardial-only ICI-associated disease."

We described a patient with an advanced NSCLC treated by atezolizumab 1200 mg every 3 weeks in combination with cabozantinib who was hospitalized for a cardiac tamponade due to a malignant pericardial effusion. Cytology has proven to be a rapid and valuable tool for diagnosis, due to information obtained by recent technologies such as high cellular fluorescence typical of malignancy.

Case report

A 69-year-old man with a stage 4 NSCLC, on treatment since 1 year, was admitted due to significant worsening of dyspnea (the New York Heart Association (NYHA) class III) and mild chest pain. The NSCLC had no EGFR, ALK, ROS, and BRAF targetable genomic alterations, and

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PDL-1 tumor expression was more than 50%. The patient had been included in the experimental arm of an open-label, phase 3, randomized clinical trial evaluating the efficacy of atezolizumab in combination with cabozantinib in metastatic NSCLC progressing after chemotherapy and an anti-PD-L1/PD-1 antibody. The patient had already received five intravenous infusions of atezolizumab (1200 mg every 3 weeks), an ICI. He was on day 97 after the first infusion.

When he was admitted at the hospital, a low voltage was seen on the electrocardiogram (see the supplemental material), and the clinical assessment was completed by a transthoracic echocardiogram (TTE) showing a cardiac tamponade due to a major pericardial effusion. Initially, an autoimmune pericarditis was considered as potential diagnosis. A therapeutic pericardiocentesis was performed and collected 1200 mL of serohemorrhagic liquid, highly suspicious of malignancy. The fluid protein content was 45 g/L, and lactate dehydrogenase (LDH) and glucose were not checked. Red blood cell count was 0.039×10^9/L. The total nucleated cell count was 2.676×10^9/L and the cellular composition was neutrophil-predominant (56%), followed by monocytes and macrophages (22%), lymphocytes (9%), mesothelial cells (6%), eosinophils (2%), and basophils (1%). Interestingly, cells suggestive of malignancy were considered, as the Sysmex XN-1000 hematology analyzer (Sysmex, Kobe, Japan) showed a wide group of highly fluorescent cells that were quite distinct from the white blood cell (WBC) clusters (Figure 1), with a high-fluorescence body fluid (HF-BF%) of 5.2% and HF-BF count of 0.132×10^9/L (no cut-off available). Cytology performed in the hematology laboratory revealed 4% neoplastic cells based on typical morphological abnormalities observed after a cytospin and the May–Grünwald–Giemsa staining method, thus allowing the diagnosis of pericardial carcinomatosis (Figure 2). Histopathologic examination confirmed 3 days later a class 5 diagnostic category highlighting the presence of isolated and clustered cells of an adenocarcinoma. The bacterial culture remained sterile.

Because the amount of newly produced pericardial fluid did not prevent removal of the catheter, we did not consider administering intrapericardial infusion of sclerosing agent (e.g. bleomycin). The antitumor treatment was temporarily discontinued because of a cardiogenic hepatic failure caused by the tamponade, resulting in mixed liver enzyme alterations. Antitumor therapy was then reinitiated after the normalization of liver enzymes a week later and the patient was discharged from hospital.

The disease further progressed on the experimental atezolizumab/cabozantinib treatment. Two follow-up TTEs found the relapse of a loculated pericardial effusion, and later, the occurrence of solid pericardial nodules on computed tomography (CT) scan confirmed the malignant origin of the pericardial effusion (Figure 3). This tumor infiltration of the pericardium was considered as secondary to the lung adenocarcinoma, as the patient initially had locally advanced

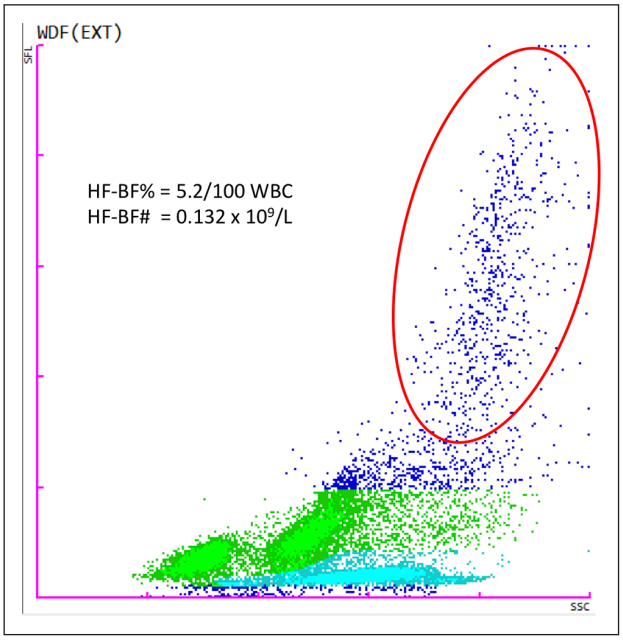

Figure 1. Body fluid scattergram. WBC differential fluorescence (WDF) scattergram of the patient's pericardial effusion showed high fluorescent cells (HF-BF# = 0.132×10^9/L). The greater dispersion of these cells reflects a wide heterogeneity of nucleic acid content and internal cell structure (red ellipse).
SFL: side fluorescence; SSC: side scatter.

disease, characterized by a lymphangitic carcinomatosis and a pleural infiltration. ICI treatment was stopped, and third-line chemotherapy was eventually initiated.

Discussion

Cytologic examination is a cornerstone for the workup of pericardial effusions, especially in hemorrhagic specimens without traumatic history as they are more likely to be malignant.[6] For malignancy detection, the analytical sensitivity is between 67% and 92%, with a high specificity of almost 100% in some studies.[7–10] Integrating valuable fluorescence information provided by hematology analyzers (e.g. XN series (Sysmex), UniCel DxH (Beckman Coulter, Brea, CA, USA), or UF-5000 (Sysmex)) could be effective for malignancy diagnosing when combined with optical microscopy as it shows good analytical performance.[11,12] When no malignant cells are found in the fluid or when a pericardiocentesis cannot be performed due to low volume effusions, a pericardial biopsy can be indicated for final diagnosis. A pericardial biopsy may be mandatory for diagnostic immunocytology or molecular testing if the pericardial fluid does not contain enough cells to perform a cell block.[7,9] The numerous cytomorphological abnormalities observed in the patient's fluid and the scarcity of inflammatory cells led to the highly probable diagnosis of pericardial carcinomatosis, which was confirmed by histopathological analysis in a second time. However, sometimes the diagnosis of malignant effusion can

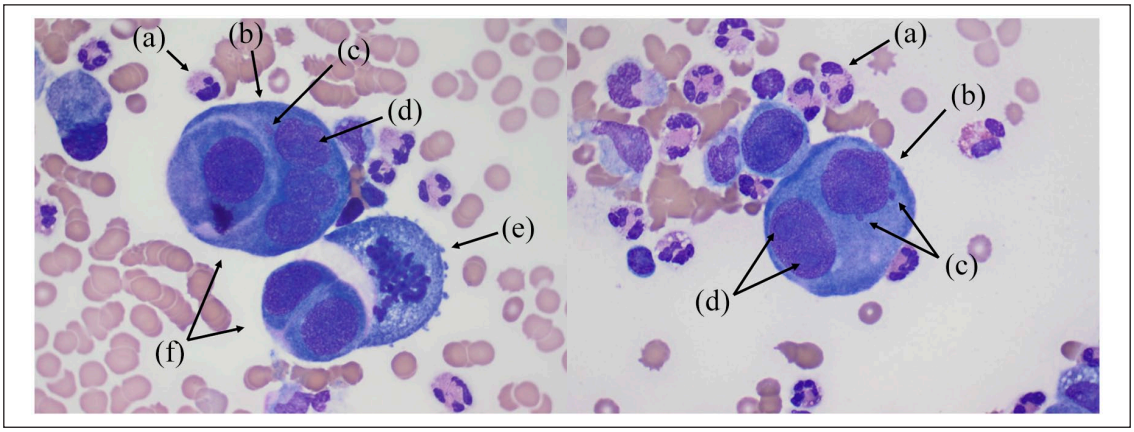

Figure 2. Cytological morphology. Cytomorphological analysis on the collected pericardial effusion was carried out after a cytospin and the May–Grünwald–Giemsa staining method. It highlighted giant basophilic cells compared to a normal neutrophil (a). Some cells accumulated numerous morphological characteristics typical of malignancy including multinuclearity (b), nuclear blebs (c), several large irregular nucleoli (d), asymmetrical mitotic figure (e), and images of cannibalism (f). No acute inflammatory cells were visualized. Magnification: 100×.

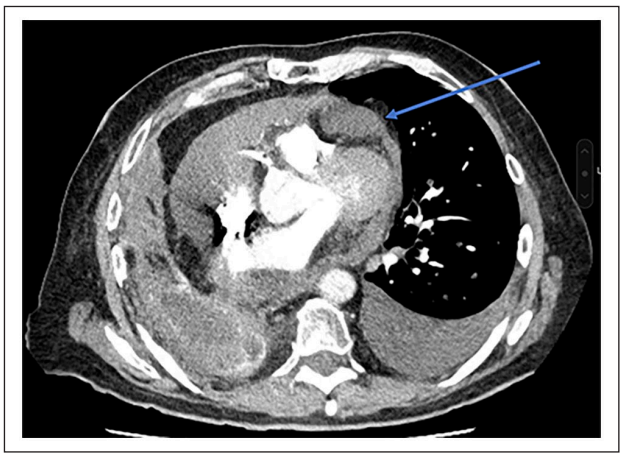

Figure 3. CT scan. Pericardial tumor nodules (blue arrow) were seen on the CT scan performed at further tumor progression 2 months after the acute cardiac failure.

be difficult, like in mesotheliomas and lymphomas, the pericardial fluid showing atypical cells. Recently, an expert consensus has defined five diagnostic categories for serous effusions, associated with an increasing probability of malignancy, in order to standardize cytopathological reports.[13] Class 1 is considered as benign and class 5 as definitely malignant, similar to histopathological examinations.

The patient's neutrophil-predominant effusion was in accordance with a recent Japan study that observed neutrophils as predominant in effusions of a population of 44 patients with carcinomatous pericarditis.[14] The authors also observed a median survival duration after drainage significantly shorter in patients with neutrophil-to-lymphocyte ratio >3.5. Although these were probably exudates, biochemical findings were not provided and the pericardial fluid WBC differential was not compared to the blood WBC differential.

The pretest probability of carcinomatous pericarditis was already high for our patient since most of the cardiac tamponades have a malignant origin, even more in patients with lung cancer. In addition, a cardiac tamponade combined with the absence of inflammatory signs as defined by Sagristà-Sauleda et al.[15] suggests the diagnosis of a malignant effusion with a likelihood ratio of 2.9.

This case of cardiac tamponade on pericardial effusion was initially suspected as "pericardial-only ICI-associated disease" as the patient had no particular cardiac alteration. The cardiac failure occurred 97 days after the first infusion, although an asymptomatic pericardial effusion was already seen on the CT scan 4 weeks earlier. A median of 40 days after ICI treatment initiation before ICI-induced pericarditis occurrence has been observed by Canale et al.[1] The authors described pericardial effusions as incidental findings detected on scheduled CT scans for disease follow-up in asymptomatic patients. Cardiotoxic effects have also been described in vascular growth factor receptor tyrosine kinase inhibitors (VEGF-TKIs), and pericardial effusion with other tyrosine kinase inhibitor (TKI) such as dasatinib has been reported.[16,17] However, cases with cabozantinib are scarce as only one has described non-tumoral pericardial effusion in a patient with renal cell carcinoma.[18] The checkpoint inhibitor was therefore more likely incriminated in our case. Nevertheless, the causal relation between the effusion and ICI has to be confirmed by pericardial fluid analysis since malignancies are the major cause of large pericardial effusions.[4]

Conclusion

Atezolizumab, an ICI, can lead to pericardial-only ICI-associated disease. For the differential diagnosis, the analysis of the pericardial fluid can offer a rapid result by the cytology performed in the hematology laboratory with

specific features for malignancy detection. The sensitivity can be optimized by integration of valuable fluorescence information. The use of standardized results for cytology is recommended.

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Author contributions

L.B., M.L., R.A., L.T., and D.R. analyzed and interpreted the biological data. G.J.-C. analyzed, interpreted, and revised the oncological data and manuscript. L.B. wrote, reviewed, and submitted the manuscript. All authors read and approved the final manuscript.

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Informed consent

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Supplemental material

Supplemental material for this article is available online.

References

1. Canale ML, Camerini A, Casolo G, et al. Incidence of pericardial effusion in patients with advanced non-small cell lung cancer receiving immunotherapy. *Adv Ther* 2020; 37(7): 3178–3184.
2. Escudier M, Cautela J, Malissen N, et al. Clinical features, management, and outcomes of immune checkpoint inhibitor–related cardiotoxicity. *Circulation* 2017; 136(21): 2085–2087.
3. Heinzerling L, Ott PA, Hodi FS, et al. Cardiotoxicity associated with CTLA4 and PD1 blocking immunotherapy. *J Immunother Cancer* 2016; 4: 50.
4. Palaskas N, Morgan J, Daigle T, et al. Targeted cancer therapies with pericardial effusions requiring pericardiocentesis focusing on immune checkpoint inhibitors. *Am J Cardiol* 2019; 123(8): 1351–1357.
5. Salem J-E, Manouchehri A, Moey M, et al. Cardiovascular toxicities associated with immune checkpoint inhibitors: an observational, retrospective, pharmacovigilance study. *Lancet Oncol* 2018; 19(12): 1579–1589.
6. Atar S, Chiu J, Forrester JS, et al. Bloody pericardial effusion in patients with cardiac tamponade. *Chest* 1999; 116(6): 1564–1569.
7. Saab J, Hoda RS, Narula N, et al. Diagnostic yield of cytopathology in evaluating pericardial effusions: clinicopathologic analysis of 419 specimens—cytology of pericardial effusions. *Cancer Cytopathol* 2017; 125(2): 128–137.
8. Kalogeraki A, Lazopoulos G, Papadakis GZ, et al. Cytology of pericardial effusion due to malignancy. *Roman J Inter Med* 2016; 54(3): 179–183.
9. Dragoescu EA and Liu L. Pericardial fluid cytology: an analysis of 128 specimens over a 6-year period. *Cancer Cytopathol* 2013; 121(5): 242–251.
10. Wiener HG, Kristensen IB, Haubek A, et al. The diagnostic value of pericardial cytology. *Acta Cytol* 1991; 35(2): 149–153.
11. Buoro S, Seghezzi M, Dominoni P, et al. Lack of harmonization in high fluorescent cell automated counts with body fluids mode in ascitic, pleural, synovial, and cerebrospinal fluids. *Int J Lab Hematol* 2019; 41(2): 277–286.
12. Cho J, Oh J, Lee S-G, et al. Performance evaluation of body fluid cellular analysis using the Beckman Coulter UniCel DxH 800, Sysmex XN-350, and UF-5000 automated cellular analyzers. *Ann Lab Med* 2020; 40(2): 122–130.
13. Pinto D, Chandra A, Crothers BA, et al. The international system for reporting serous fluid cytopathology: diagnostic categories and clinical management. *J Am Soc Cytopathol* 2020; 9(6): 469–477.
14. Oyakawa T, Muraoka N, Iida K, et al. Characteristics of cellular composition in malignant pericardial effusion and its association with the clinical course of carcinomatous pericarditis. *Japan J Clin Oncol* 2018; 48(3): 291–294.
15. Sagristà-Sauleda J, Mercé J, Permanyer-Miralda G, et al. Clinical clues to the causes of large pericardial effusions. *The American Journal of Medicine* 2000; 109(2): 95–101.
16. Iacovelli R, Ciccarese C, Fornarini G, et al. Cabozantinib-related cardiotoxicity: a prospective analysis in a real-world cohort of metastatic renal cell carcinoma patients. *Br J Clin Pharmacol* 2019; 85(6): 1283–1289.
17. Eskazan AE, Soysal T, Ongoren S, et al. Pleural and pericardial effusions in chronic myeloid leukemia patients receiving low-dose dasatinib therapy. *Haematologica* 2011; 96(3): e15.
18. Cabozantinib: acute cardiogenic shock—case report. *React Week* 2020; 1795(1): 76.