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Cytologically malignant lymphoid pericardial effusion with benign clinical outcome

Report of two cases

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Summary

Background: Isolated malignant pericardial effusion is a manifestation of primary cardiac lymphoma (PCL) and primary effusion lymphoma (PEL), rare types of non-Hodgkin's lymphoma (NHL). The diagnosis is based on different cytological methods and analyses including DNA-image cytometry (ICM-DNA). DNA-aneuploidy has been reported to be highly specific for malignancy.

Case descriptions and results: A 75-year-old man and a 66-year-old woman underwent urgent pericardiocentesis for cardiac tamponade due to large pericardial effusion. In both patients pericardial fluid analysis showed highly atypical blastic lymphoid cells expressing CD45 (both patients) and CD20 (assessed only in one patient), and ICM-DNA revealed significant DNA-aneuploidy (2c deviation index 9.22 and 10.73 respectively, 75% and 60% respectively of the target nuclei in aneuploid areas). Extensive staging examinations did not identify any other tumour manifestation. Although in neither of the two patients systemic chemotherapy was administered, both were free of cancer after a follow-up of ten and nine years respectively.

Conclusions: Despite the highly atypical cytomorphology including unequivocal DNA-aneuploidy, long-term survival in both patients strongly suggests that pronounced reactive lymphocytic changes are probably due to viral pericarditis rather than PCL or PEL as underlying conditions. It seems that DNA-aneuploidy may be not absolutely specific for the detection of malignant lymphoid cells in pericardial fluid.

Key words: pericardial effusion; cytology; DNA image cytometry; aneuploidy; specificity; reactive

Introduction

Cardiac involvement of systemic lymphoma has been reported in up to 20% of cases. However, primary cardiac lymphoma (PCL) defined as non-Hodgkin's lymphoma (NHL), which involves only the heart and the pericardium, is a very rare entity [1, 2]. PCL typically occurs in patients infected with the human immunodeficiency virus (HIV) or in elderly apparently immunocompetent people [1]. The tumour formation predominantly originates from the right-sided chambers of the heart diffusely infiltrating the cardiac tissue. Pericardial involvement with massive effusion is a typical and sometimes isolated manifestation of PCL [1, 2]. The same clinical picture may be observed in patients with primary effusion lymphoma (PEL), a recently described type of NHL characterised by growth in serous body cavities without detectable tumour masses [3–5]. Primary effusion lymphoma predominantly occurs in HIV-positive men and is usually associated with human herpes virus 8 (HHV 8) infection of the tumour clone, which may be co-infected by Epstein-Barr virus (EBV). However, there are some reports about PEL in HIV-negative elderly people and organ transplantation recipients, and HHV 8-negative PEL has also been found [3, 4, 6].

In both PCL and PEL pericardial fluid analysis may be the key to the diagnosis of malignancy. The currently employed diagnostic methods include cytology of the effusion sediment, immunocytochemistry, DNA image cytometry (ICM-DNA), polymerase-chain-reaction (PCR) and cytogenetic analysis [1, 5, 7–14]. Measurement of nuclear DNA by ICM-DNA has been shown to

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improve diagnostic accuracy of conventional cytology for the detection of malignant cells in body cavity effusions [11, 12]. Whereas DNA-aneuploidy has a moderate sensitivity for the identification of malignant cells, the positive predictive value of DNA-aneuploidy for the detection of malignant cells is very high [11, 12].

Case reports

Case 1

In 1993, a 75-year old man presenting with new onset signs of right heart failure underwent pericardiocentesis for large pericardial effusion. Analysis of pericardial fluid revealed highly atypical large lymphoid cells (figure 1) with immunocytochemical expression of leukocyte common antigen (CD45) and the B-cell marker CD20. These cells showed no reaction for pancytokeratin (Lu-5) and the T-cell marker CD3, the latter being expressed by the concomitant normal lymphocyte population. Additionally, ICM-DNA was performed according to the available technique (Zeiss-Kontron/CIRES 3.1 workstation) and the standards of diagnostic ICM-DNA at that time, revealing significant DNA-aneuploidy (figure 2). Therefore, NHL was suspected. Values for serum creatinine, albumin, and thyroid-stimulating hormone were within the normal ranges. The following examinations including thoracoabdominal computed tomography, bronchoscopy, oesophagogastroscopy, bone marrow aspiration, and lumbar puncture were normal. One week later, echocardiography showed a small residual pericardial effusion, a dilated left atrium, and a slightly impaired left ventricular systolic function. After intrapericardial administration of bleomycin the patient refused to undergo systemic chemotherapy, and ten years later he was still alive without signs of a tumour.

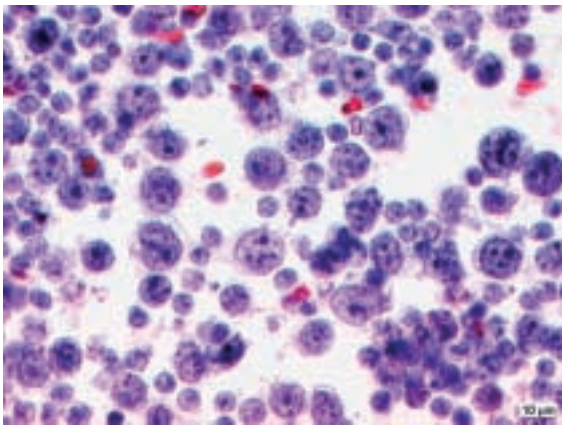

Figure 1

Pericardial fluid specimen of patient (1) revealing numerous highly atypical lymphoid cells with high nuclear/cytoplasmic ratios, irregular nuclear structure and large polymorphic nucleoli (Papanicolaou staining, original magnification x 400).

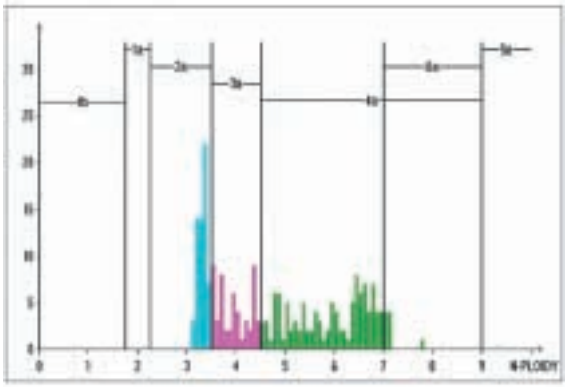

Figure 2

DNA histogram of pericardial effusion in patient (1) revealing significant DNA-aneuploidy. Abcissa: DNA values in c-units; ordinate: number of measured nuclei. DNA mean value 4.64 (normal 2.0), DNA index 2.32 (normal 1.0), 2c deviation index 9.22 (normal 0), 5c exceeding events 99 (normal 0), 9c exceeding events 0 (normal 0). Aneuploid DNA stemline in the 3c area, overall 75% aneuploid target cells with complete lack of diploid nuclei.

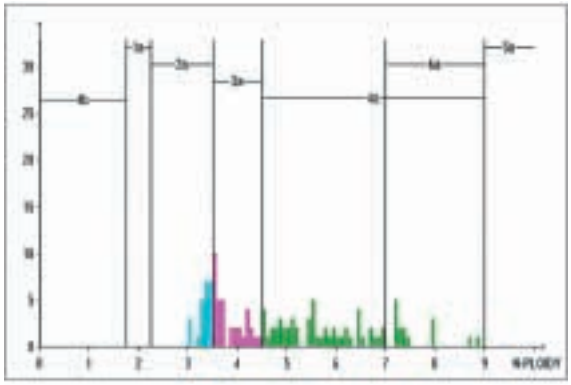

Figure 3

DNA histogram of pericardial fluid in patient (2) revealing significant DNA aneuploidy. Abcissa: DNA values in c-units; ordinate: number of measured nuclei. DNA mean value 4.93 (normal 2.0), DNA index 2.47 (normal 1.0), 2c deviation index 10.73 (normal 0), 5c exceeding events 52 (normal 0), 9c exceeding events 0 (normal 0). Aneuploid DNA stemline in the 3c area, overall 60% aneuploid target cells with complete lack of diploid nuclei.

Case 2

In January 1995, a previously healthy 66-year-old woman was admitted with rapidly developing signs of right heart failure. Transthoracic echocardiography showed a large circumferential pericardial effusion, but was otherwise within normal limits. Due to evolving pericardial tamponade urgent pericardiocentesis was performed. The pericardial fluid was lymphocyte-rich, and cytology showed highly atypical large lymphoid cells with immunocytochemical expression of CD45 and negative reaction for Lu-5. ICM-DNA revealed significant aneuploidy (figure 3). Therefore, high-grade malignant lymphoma was strongly suspected. Cultures did not yield bacterial growth, and no acid-fast bacilli were detected. A tuberculin skin test was negative. Values for serum creatinine, albumin, and thyroid-stimulating hormone were within the normal ranges. Further examinations including computed tomography of the chest, abdomen and pelvis, abdominal sonography, left-sided pleurocentesis, protein electrophoresis, and bone marrow aspiration did not give evidence of any underlying tumour. Subsequently, thoracoscopic creation of a pericardial window was performed, and a biopsy specimen was taken, revealing chronic pericardial inflammation without tumour infiltration. No specific treatment was administered, and the patient was discharged. Follow-up echocardiography six months later showed signs of hypertensive heart disease in absence of pericardial effusion. Nine years later the patient was still alive and free of cancer.

Discussion

We herein present two patients in whom, based on the highly atypical cytomorphology and unequivocal DNA-aneuploidy of the pericardial fluid specimens high-grade NHL was diagnosed, and whose clinical courses retrospectively question the clinical significance of the cytological diagnosis of lymphoid malignancy.

Since an extensive tumour search in both patients did not reveal enlarged lymph nodes or tumour formations, disseminated lymphoma was very unlikely to be present. Thus, PCL and PEL have to be considered as possible underlying conditions. The latter entity however, had not been described when our patients were evaluated, but retrospectively this diagnosis would well fit the findings at least in one patient. Both PCL and PEL may occur in elderly people, even in absence of HIV infection or other causes of immunosuppression [15, 16], and can present as large, quickly evolving pericardial effusion causing cardiac tamponade [2]. The fact that transthoracic echocardiography did not show any intracardiac masses, does not rule out the presence of PCL. Transoesphageal echocardiography and magnetic resonance imaging are more appropriate tools for the diagnosis of PCL, especially for those located around the pulmonary vessels, superior vena cava, and the upper part of the right atrium [1]. In PEL the tumour is restricted to the serous cavity (eg pleural space, pericardium), and thickened serous membranes are the only detectable feature except for the very rare cases of extraserous spread of PEL [4, 17].

The most powerful argument against malignancy in the presented patients is long-term survival without systemic chemotherapy. Both PCL and PEL are rapidly progressive NHL associated with a very poor prognosis due to arrhythmia, sudden death, and intractable heart failure [1–4]. To the best of our knowledge, long-term survival in PCL without systemic polychemotherapy has not yet been reported [15]. In contrast, there are at least three patients with HIV- and HHV-8-associated PEL, in whom long-term survival was achieved without chemotherapy [2, 18, 19]. In two of these HIV-infected patients remission of PEL was attributed to a simultaneous effect of highly-active-antiretroviral therapy (HAART) on HIV as well as HHV-8 replication with subsequent HIV as well as tumour control [2, 18]. In the third case HAART failed to control PEL [19]. However, in this patient remission of PEL was achieved with interferon-α and cidofovir, both known to be effective agents against HHV-8 [19].

In our patients tests to detect antibodies against HIV were not performed. In view of their clinical course without antiretroviral therapy the probability of HIV infection in the presented patients is very low however. In addition, they did not receive any antiviral therapy with possible effects on lymphoma-inducing viruses. The intrapericardial administration of bleomycin in the first patient did probably not have any impact on survival. Although remission of PEL without chemotherapy in HIV-negative patients has not been reported yet, one could theoretically speculate that PEL resolved spontaneously in the second patient (case 2). In the first patient (case 1) the expression of the B-cell marker CD20 speaks against the presence of PEL as the phenotypic expression of B-cell lineage-restricted antigens (eg CD20) is almost invariably absent despite their B-cell genotype [3, 5, 6, 16, 17]. Thus, even relying on a very speculative assumption, only one of the two cases can be explained by the current knowledge about PEL and PCL.

Although the diagnosis of PEL cannot be completely ruled out, an underlying benign condition mimicking exactly the morphology of NHL, seems to be a more likely explanation. The most intriguing feature in this context is the unequivocal DNA-aneuploidy. When comparing the typical DNA histogram of lymphocytes in the pericardial fluid of a patient suffering from viral pericarditis with those of the presented patients, clear differences concerning ploidy grade are seen (figure 4). To the best of our knowledge, such a pattern of massive DNA-aneuploidy has not been reported in the setting of a benign condition. Several studies evaluating the impact of DNA flow cytometry or ICM-DNA on the diagnosis of malignancy in effusion cytology have revealed a low to moderate sensitivity of DNA-aneuploidy for the detection of malignant cells [12, 13, 21], whereas the values for the specificity of DNA-euploidy for benignity and the positive predictive value of DNA-aneuploidy for malignancy respectively were reported to range between 94 and 100% [8, 11–13, 20, 21]. However, in most series the percentage of pericardial effu-

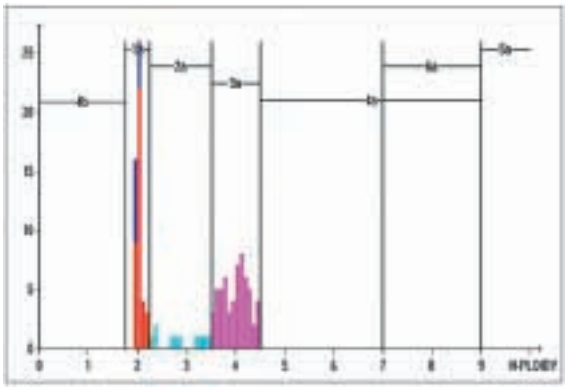

Figure 4
DNA histogram of pericardial effusion of a patient with proven viral pericarditis (echovirus type IV) revealing the typical DNA profile of a highly proliferating cell population and nuclear inclusion of viral DNA respectively. Abcissa: DNA values in c-units; ordinate: number of measured nuclei. DNA mean value 3.2 (normal 2.0), DNA index 1.6 (normal 1.0), 2c deviation index 2.32 (normal 0), 5c exceeding events 0 (normal 0), 9c exceeding events 0 (normal 0). 91.5% of the measured nuclei with an euploid DNA content.

sions among the examined body cavity fluids as well as lymphoma among the studied malignancies was very low, and thus application of these study results on the presented cases is limited. In an analysis of 61 pericardial fluid specimens flow cytometry was found to have a sensitivity and specificity of 80% and 100% respectively [21]. In this study however, effusions cytology was used as the gold standard, and clinical data were not considered [21]. A similar study using ICM-DNA is not available, but the diagnostic accuracy was clearly better for ICM-DNA as compared to flow cytometry in the setting of body cavity fluid analysis [12, 13].

When looking at factors contributing to false-positive results of DNA ploidy analysis, tuberculosis has been identified as a major cause [13, 22]. By analysing pleural effusions from 92 patients Rodriguez de Castro and co-workers found aneuploid cells in seven of 22 tuberculous effusion specimens (74.5% specificity of aneuploidy for the diagnosis of malignancy) [22]. Tests to detect tuberculosis had been negative in both patients, and false-negative results are unlikely due to the favourable outcome without antituberculous therapy. Other possible sources of false positive results of DNA-ICM are technical in nature including autolysis after delayed sample preparation and aggregated cells mimicking aneuploid cells [23, 24]. These technical problems cannot provide sufficient explanation for the massive and unequivocal DNA-aneuploidy in the presented cases however. Although comparable cases have not been reported before, we assume that a not yet described form of reactive lymphocytosis induced by a benign condition, probably viral pericarditis, might have mimicked NHL in the presented cases. Similarly to the very atypical morphology seen in lymph node histology in infectious mononucleosis, the apparently malignant pericardial effusion cytology could have resulted from EBV-associated pericarditis.

As pointed out before, there are several arguments against PEL and PCL as underlying conditions. Nevertheless, apart from benign lesions with false-positive cytomorphology, the possibility of a truly neoplastic, but spontaneously resolving lymphoproliferative disorder cannot be completely excluded. The present cases remind one of the entity called lymphomatoid papulosis, a clonal and neoplastic, but clinically indolent cutaneous T-cell lymphoproliferative disorder, which is histologically malignant but often self regressive [25]. In addition, there are recent reports on so-called senile EBV-associated lymphoproliferative diseases, which may be transient and also can involve extranodal sites including serous cavities. However, isolated pericardial involvement has not been described yet, and spontaneous resolution without specific therapy is very rare in these pathologies [26]. Although we cannot completely exclude the presence of transient, truly malignant conditions, this seems to be a rather speculative hypothesis.

The complete documentation of the clinical course including cytological examination with ploidy analysis as well as long-term follow-up are the strengths of our study. However, due to the long follow-up period some of the reported cytological methods are not the today's state-of-the-art, and newer methods such as PCR, immunocytochemistry with a broad panel of antibodies and cytogenetic analysis have not been used. Unfortunately, there is no material available to perform additional analysis such as studies for EBV or HHV-8, which might have provided further insights. Thus, the exact nature of the lesions in the presented cases will never be determined.

In conclusion, reactive pericardial effusion lymphocytosis may present as a highly atypical cell population with all features of malignant lymphoma including significant aneuploidy. Therefore, even unequivocal DNA-aneuploidy as revealed by ICM-DNA from pericardial fluid analysis cannot be considered absolutely specific for the presence of a clinically malignant condition.

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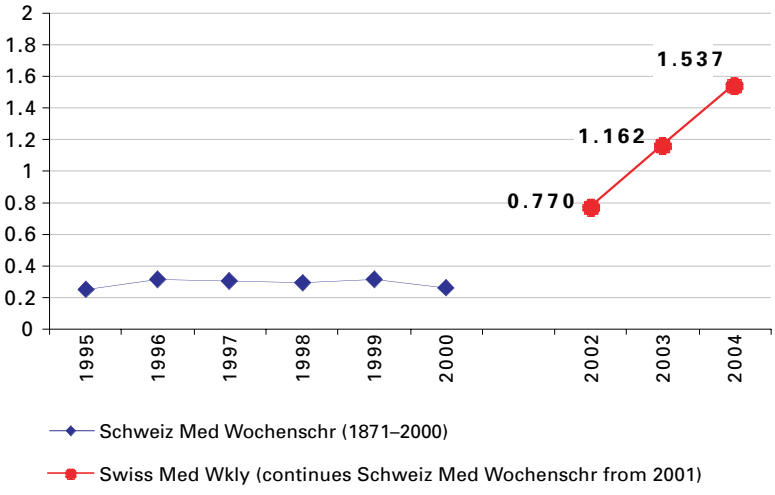

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