OPEN ACCESS

Case Report

Pyothorax-associated lymphoma (PAL): report and review of a rare entity

Pyothorax assoziiertes Lymphom (PAL): Kasuistik und Review einer seltenen Erkrankung

Abstract

Pyothorax-associated lymphoma (PAL) is a rare haematological malignancy often associated with artificial pneumothorax due to the treatment of pulmonary tuberculosis. A 76 year old man with chronic tube-drained pyothorax and a history of artificial pneumothorax for pulmonary tuberculosis was admitted to our hospital because of progressive right thoracic pain, weight loss, and pyrexia. After clinical examination and imaging processes a chest wall tumour anterior on the right side was diagnosed as well as a persisting pyothorax. Surgery was performed to resect the tumour and drain the pleural cavity. A diagnosis of a high grade B-cell lymphoma was established after histological examination of the surgical biopsy. Epstein-Barr virus (EBV) was identified in the tumour by immunocytochemical and molecular methods. Additional gastric involvement of B-cell lymphoma could be diagnosed by gastroscopy because of postoperative gastrointestinal bleeding. The patient received chemotherapy with 2 courses of cyclophosphamide, doxorubicin, vincristine and prednisolone (CHOP). The response was favourable initially, but 2 months later the patient died because of lymphoma progression.
Most cases of PAL have been described by Japanese investigators and only a few cases are reported in Western countries. To the best of our knowledge this case of PAL is the first to be documented in Germany. Awareness of this rare entity, together with diligent histological examination, in patients with chronic pyothorax are essential for a correct diagnosis and correct early treatment.

Keywords: Pyothorax-assoziiertes Lymphom (PAL), Empyem, Tuberkulose, B-Zell-Lymphom, artifizielle Pneumothorax, pyothorax-associated lymphoma, empyema, tuberculosis, B cell lymphoma, artificial pneumothorax

Katrin Welcker[1]
Masaki Nakashima[1]
Klaus-Dieter Diemel[1]
Lutz Welker[1]
Jürgen Galle[2]
Hartmut Merz[3]
Detlev Branscheid[1]

1 Department of Thoracic Surgery, Krankenhaus Großhansdorf, Zentrum für Pneumologie und Thoraxchirurgie, Großhansdorf, Germany

2 Pathologie Forschungszentrum Borstel, Borstel, Germany

3 Institut für Pathologie, Universitätsklinikum Schleswig-Holstein, Campus Lübeck, Lübeck, Germany

Zusammenfassung

Das Pyothorax-assoziierte Lymphom (PAL) stellt eine seltene maligne Erkrankung dar, die sich häufig auf der Basis einer Pneumothoraxbehandlung nach Tuberkulose entwickelt.
Ein 76 jähriger Mann mit einem chronischen Pleuraempyem auf der Basis einer artifiziellen Pneumothoraxtherapie nach stattgehabter Tuberkulose wurde mit zunehmenden rechts-thorakalen Schmerzen, Gewichtsabnahme und Fieber stationär aufgenommen. Nach klinischer Untersuchung und bildgebenden Verfahren wurde die Diagnose eines Tumors der rechten Thoraxwand bei weiterhin bestehendem Pyothorax gestellt. Nach chirurgischer Resektion des Tumors und Debridement des Pyothorax ergab sich die Diagnose eines hoch malignen Epstein-Barr-Virus (EBV) positiven B-Zell-Lymphoms. Zusätzlich gelang der gastroskopische Nachweis des B-Zell-Lymphoms im Magen bei postoperativ aufgetretener oberer gastrointestinaler Blutung. Der Patient erhielt postoperativ 2 Zyklen Chemotherapie nach dem CHOP-Schema (Cyclo-

phosphamid, Doxorubicin, Vincristin und Prednisolon). Nach primärem Erfolg der Chemotherapie starb der Patient 2 Monate später an einer Progression des Tumorleidens.
PAL stellt eine vor allem von japanischen Autoren berichtete Entität dar. Nur wenige europäische Fälle sind bisher beschrieben worden. Nach unserem Kenntnisstand ist dies der erste in Deutschland dokumentierte Fall.
Die Differentialdiagnose des PAL verbunden mit einer genauen histologischen Untersuchung sollte bei Patienten mit chronischem Pyothorax immer in Erwägung gezogen werden, um durch eine frühzeitige Diagnosestellung die Patienten der adäquaten Therapie zuführen zu können.

Introduction

We present the case of a 76 year old man with non-Hodgkin´s lymphoma. A tumour developed in the pleural cavity after a long-term history of pyothorax following artificial pneumothorax for pleuropulmonary tuberculosis. Most cases of this entity called pyothorax-associated lymphoma (PAL) have been described by Japanese investigators. Only a few cases have been reported in Western countries. To the best of our knowledge this case of PAL is the first to be documented in Germany.

Case presentation

Our patient, a 76 year old male, fell ill with pulmonary tuberculosis at the age of 18 and was treated surgically by artificial pneumothorax. He later worked in a shipyard for 20 years and was exposed to asbestos.
58 years after the diagnosis of tuberculosis, he was presented to our hospital with exacerbation of a pyothorax persisting since 30 years. The pyothorax was treated by video-assisted thoracoscopic tube drainage and he required recurrent drainage of the pleural cavity. Initially, he improved, but 4 months later his symptoms progressively worsened, subsequently, he began to complain of chest pain, recurrent pyrexia (up to 40 °C), and 20 kg loss of weight, as well as painful swelling of the right lateral hemithorax. The drainage of the right hemithorax through the previously inserted chest tube was sufficient. There was no associated lymphadenopathy or hepatosplenomegaly. The laboratory findings on admission were as follows: Haemoglobin 8.7 g/dl, CRP 140.3 µm/l. There was a leucocytosis of 11.300/mm^3 with no leukaemic cells identified. Further laboratory findings were generally within normal limits. A microbiological analysis of the pyothorax isolated enterococcus species and staphylococcus epidermidis. Mycobacterium tuberculosis could not be identified.
The chest x-ray showed a massive shadow in the right lower part of the thorax adjacent to the chest wall. A CT scan of the chest revealed atelectasis of the lung, a massive pyothorax surrounded by calcification, and a round mass at the lower lateral part of the pyothorax involving all layers of the chest wall. The mass measured 3 cm in diameter (Figure 1).

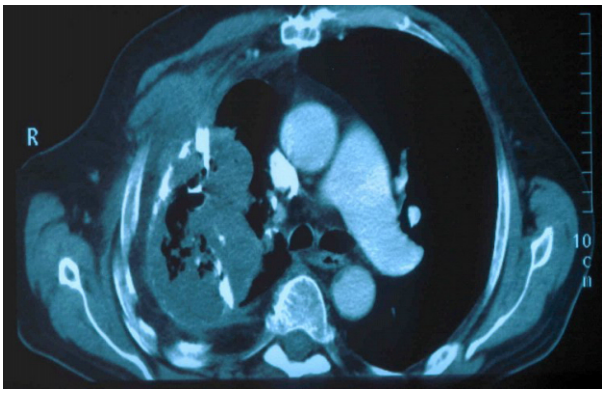

Figure 1: Chest x-ray showing a massive pyothorax surrounded by calcification and a round mass at the lower part of the pyothorax wall involving all layers of the chest wall anterolateral.

Surgery was performed for diagnosis as a malignant mesothelioma was suspected. At operation tumour infiltration of all layers of the chest wall was confirmed. After anterolateral thoracotomy, the tumour mass was resected and the fibrinopurulent debris were removed. Necrotic lung tissue was excised and a large-lumen chest drain was inserted (Figure 2).

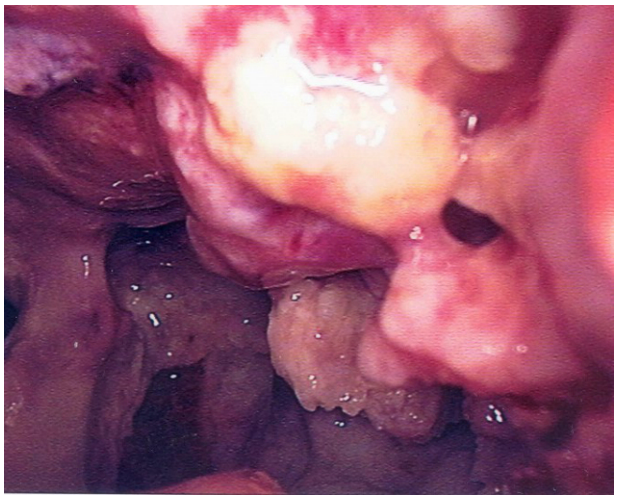

Figure 2: Intraoperative view of the pleural cavity. Tumour masses at the chest wall and fibri-nopurulent debris are shown.

The histological and immunohistological findings showed a marked fibrous thickening of the pleural tissue surrounding the tumour mass with presence of non-neoplastic inflammatory cells. The tumour was classified as a diffuse large B-cell lymphoma with uniform highly pleomorphic,

frequently round to ovoid large blasts, with centrally located one or more irregular shaped nucleoli and deeply basophilic, sometimes abundant cytoplasm with rare vacuoles in occasional cells. The immunophenotype of the lymphatic cells corresponds to a large B-cell lymphoma with plasmoblast features: CD20+, CD79+, CD30+, CD38+, IRF4(Mum1)+. In situ hybridisation for Epstein Barr virus small nuclear RNAs revealed strong nuclear positivity in all tumor cells (Figure 3, Figure 4).

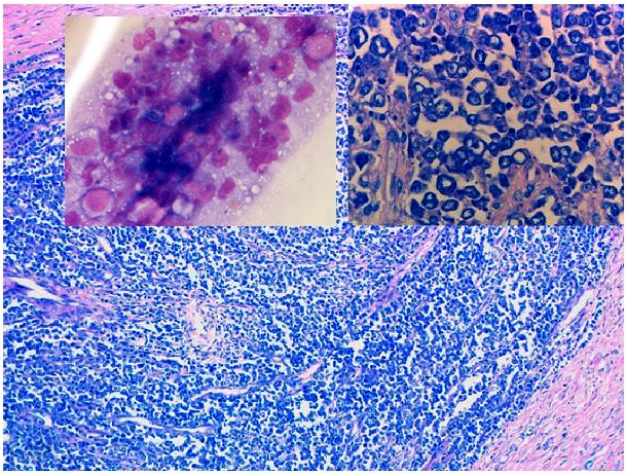

Figure 3: Histological specimen of the infiltration of the chest wall. The tumour consists of medium sized to large lymphoma cells with round to slightly pleomorphic nuclei with plasmoblastic features, the cells appear more uniform in the histological section than in the cytospin preparation with round or ovoid nuclei and more or less abundant basophilic cytoplasm. Cytology [above left] is reminiscent of primary effusion lymphoma, however the clinical presentation distinguished this form of lymphoma from primary lymphoma by a large pleural mass and dissemination.

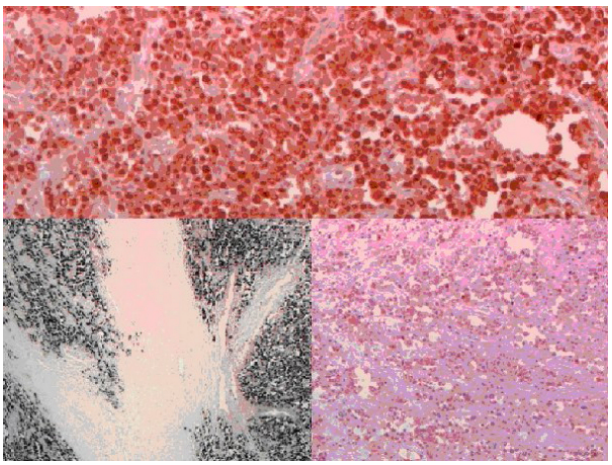

**Figure 4: [above] Immunohistochemistry shows strong expression of IRF-4, a transcription factor of plasmocytic/plasmoblastic differentiation.
[below left] Strong nuclear positively Epstein-Barr-virus RNA [EBER] demonstrated by in situ hybridisation.
[below right] Tumor cells show weak, moderate, and strong stainig for CD30**

Human herpesvirus 8 (HHV-8) could not be identified by polymerase chain reaction in situ hybridisation.

Five days postoperatively, the patient suffered from hematemesis. A tumour of the greater curvature of the stomach was visualised through gastroscopy and biopsies were taken. Histology revealed the same type of a high grade B-cell lymphoma as in the chest wall.
The patient subsequently received 2 courses of chemotherapy with cyclophosphamide, doxorubicin, vincristine and prednisolone (CHOP). The chest tube remained in place during the chemotherapy. Initially, there was some improvement in the patient's clinical condition but unfortunately, two months later he died of lymphoma progression.

Discussion

Malignant lymphoma in the chest wall after therapeutic pneumothorax is a rare condition in Europe but its prevalence in Western countries maybe underestimated. Although pyothorax is a common complication of treatment of tuberculosis, the combination of malignant pleural lymphoma and long lasting pyothorax is relatively unknown and, to the best of our knowledge, no case has till now been reported in Germany.
In 1985 the term pyothorax-associated lymphoma (PAL) was first proposed by Japanese authors for the development of pleural lymphoma against a background of longstanding inflammation in chronic pyothorax [1]. Since then, most cases have been described by Japanese investigators. Nakatsuka reviewed 106 cases of PAL collected through a nationwide survey in Japan during a period of 28 years until 2000 [2]. Jardin found six PAL among 1,038 lymphomata (a prevalence of 0.6%) during a retrospective study of 10 years at a French hospital [3]. Since then, only 23 cases have been reported, mainly from France or Italy [4], [5], [6], [7], [8], [9], [10].
Approximately 80% of the patients with PAL underwent an artificial pneumothorax procedure in the treatment of pulmonary tuberculosis. This surgical technique was originally established in Western countries but was more widely performed in Japan. This could be the reason why more cases of PAL are reported in Japan. It is thought that artificial pneumothorax causes chronic, non-healing inflammation in the pleural cavity which, in turn, may result in the development of PAL.
The specific type of lymphoma in all cases of PAL is a Non-Hodgkin lymphoma. The most common cases were diffuse large B-cell lymphoma expressing CD20, CD30, CD45, CD79a and/or CD138 [11], [12].
In 1993, Japanese investigators were the first to identify an association between Epstein-Barr virus (EBV) and development of PAL. The primary effusion from the lymphoma in 70% of PAL cases was positive for EBV. This indicates a possible link between EBV infection and PAL and to primary effusion lymphomes (body cavity lymphoma) [13], [14].
EBV-infected PAL cell line designated PAL-1 has been established. The cell line co-expresses CD20 molecules. This represents the first example of EBV integration in

PAL and may allow the study of the potential role of integrated viral infection in the development of PAL. Localised immunosuppression induced by chronic inflammation or immunosuppressive cytokines (IL6 and IL10) may favour the clonal proliferation of EBV-infected B-cells [15].
The presence of human herpesvirus 8 (HHV-8) has been consistently reported in the primary effusion of lymphoma and in some cases of PAL, HHV-8 can be found. This indicates that HHV-8 is not an obligate pathogen, necessary for production of the malignant effusion, but may contribute to it by the secretion of specific cytokines like IL-10 and IL-6.
Non-contiguous metastatic involvement of PAL is usually seen in the lymph nodes. Involvement of other organs such as the stomach are extremely rare [16].
Patients with incidentally diagnosed PAL have initially chronic pyothorax complicated with malignancy and the diagnosis has been clarified by histological examination after tumour resection [17].
The most common complications throughout the clinical course of PAL are pneumonia, relapse of active inflammation in the empyema space or severe sepsis. Other complications are respiratory failure, bone marrow involvement and haemorrhage.
Malignant mesothelioma with extension to the adjacent tissues and chest wall must bee considered as differential diagnosis, especially in case of exposure to asbestos. Long-term pleural inflammation is an etiological factor for the development of soft-tissue sarcoma of the pleura such as malignant fibrous histocytoma or angiosarcoma [18], [19].
Lymphoma usually responds to chemotherapy but in patients with PAL, chemotherapy is sometimes difficult to perform because of persistent pyothorax. Some authors prefer open window thoracostomy as an effective management of the pyothorax prior to and during chemotherapy. The most common chemotherapeutic agents are cyclophosphamide, doxorubicin, vincristine and prednisolone in the CHOP scheme [20], [21].
Adjuvant radiotherapy of 50 Gy with wide margins is recommended in the treatment of PAL. The EBV load could be decreased by additional radiotherapy. The use of CT scan is recommended in the follow up of patients after adjuvant radiotherapy. Recurrence occurs as mass shadow in 85% of the patients. It is also reported that CT scan may be of some use in the detection of lymphomatous masses in other extranodal sites. Overall prognosis of patients with PAL is poor with a 5-year survival rate of 21%. Those who received chemotherapy and/or radiotherapy have higher 5-year survival rates [22], [23].

Conclusions

Even if PAL is a rare condition in Western countries, we should be aware of the possibility of PAL in patients with EBV positive tuberculous pyothorax. In particular, this possibility should be considered in patients with fever or chest pain and long-term tuberculous pyothorax.

References

1. Aozasa K, Tsujiimoto M, Sakurai M. Non-Hodgkin´s lymphomas in Osaka, Japan. Eur J Cancer Oncol. 1985; 21:487-92.
2. Nakatsuka S, Yao M, Hoshida Y, Yamamoto S, Iuchi K, Aozasa K. Pyothorax-associated lymphoma: a review of 106 cases. J Clin Oncol. 2002; 20(20):4255-60.
3. Jardin F, Stamatoullas A, Buchonnet G, Duval C, Dujon A, Picquenot JM, Nouvet G, Tilly H. Primary pleural lymphoma after collapse therapy: modern aspects of an historic disease. Rev Med Interne. 1999; 20(11):985-91.
4. Borrelly J, Sebbag H, Vignaud JM. False empyema after artificial pneumothorax. An original entity: type B non Hodgkin malignant lym-phoma. Ann Chir.(France) 1996; 50(5):405-8.
5. Petitjean B, Jardin F, Joly B, Martin-Garcia N, Tilly H, Picquenot JM, Briere J, Danel C, Mehaut S, Abd-AL Samad I, Copie-Bergman C, Del-fau-Larue MH, Gaulard P. Pyothorax-associated Lymphoma: a peculiar clinicupahtologic entity derived from B cells at late stage of differentia-tion and with occasional aberrant dual B- and T-cell phenotype. Am J Surg Pathol. 2002; 26(6):724-32.
6. Ascoli V, Lo-Coco F. Body cavity lymphoma. Curr Opin Pulm Med. 2002; 8(4):317-22.
7. Ascani S, Piccioli M, Poggi S, Briskomatis A, Bolis GB, Liberati F, Frongillo R, Caramatti C, Fraternali-Orcioni G, Gamneri B, Zinzani PL, Lazzi S, Leoncini L, O´leary J, Piccaluga PP, Pileri SA. Pyothorax-associated lymphoma: description of the first two cases detected in Italy. Ann Oncol. 1997; 8(11):1133-8.
8. Taniere P, Manai A, Charpentier R, Terdjman P, Boucheron S, Cordier JF, Berger F. Pyothorax-associated lymphoma: relationship with Epstein-Barr virus, human herpes virus-8 and body cavity-based high grade lymphoma. Eur Respir J. 1998; 11(3):779-83.
9. Aozaka K, Naka N, Tomita Y, Ohsawa M, Kanno H, Uchida A, Ono K. Angiosarkoma developping from chronic pyothorax. Mod Path. 1994; 7(9):906-11.
10. Androulaki A, Drakos E, Hatzianastassious D, Vgenopoulou S, Gazouli M, Korkolopoulou P, Patsouris E, Dosios T. Pyothorax.associated lymphoma [PAL]: a western case with marked angiocentricity and re-view of the literature. Histopathology 2004; 44(1):69-76.
11. Daibata M, Taguchi T, Nemoto Y, Saito T, Machida H, Imai S, Miyoshi I, Taguchi H. Epstein-Barr virus (EBV)-positive pyothorax-associated lymphoma (PAL): chromosomal integration of EBV in a novel CD2-positive PAL B-cell line. Br J Heamatol. 2002; 117(3):546-57.
12. Kim Y, Lee SW, Choi HY, Im SA, Won T, Han WS. A case of pyothorax-associated lymphoma simulating empyema necessitates. Clin Imaging. 2003; 27(3):162-5.
13. Fukayama M, Ibuka T, Hayashi Y. Epstein-Barr virus in pyothorax associated pleural lymphoma. Am J Pathol.1993; 143:1044-9.
14. Kanno H, Aozasa K. Pyothorax-associated lymphoma: EBV-positive lymphoma developing in immunocompetent patients. Nippon Rinsho (Japan). 1997; 55(2):436-40.
15. Copie-Bergmann C, Niedobitek G, Mangham DC, Selves J, Baloch K, Diss TC, Knowles DN, Delsol G, Isaacson PG. Epstein-Barr virus in -cell lymphomas associated with chronic supporative inflammation. J Pathol.1997; 183(3):287-92.
16. O´Donovan M, Silva I, Uhlmann V, Bermingham N, Luttich K, Martin C, Sheils O, Killalea A, Kenny C, Pileri S, O´Leary JJ. Expression profile of human herpesvirus 8 (HHV-8) in pyothorax associated lymphoma and in effusion lymphoma. Mol Pathol. 2001; 54(2):80-5.
17. Hsu NY, Chen CY, Pan ST, Hsu CP. Pleural non-Hodgkin´s lymphoma arising in a patient with a chronic pyothorax. Thorax. 1996; 51(1):103-4.

18. Ueda T, Tsutani H. Primary extranodal malignant lymphoma. Nippon Rinsho (Japan). 2000; 58(3):673-6.

19. Lui PC, Ng WK, Yam LY, Wong WW, Tai YP. Pyothorax-associated large B cell lymphoma: a case report with emphasis on the potential di-agnostic challenge. Hong Kong Med J (China). 2002; 8(5):359-62

20. Yoshitomi A, Chida K, Suda T, Kuwata H, Todate A, Tsukamoto K, Nakamura H, Takahashi T, Suzuki K. Pyothorax associated lymphoma treated by chemotherapy after thoracostomy. Nihon Kokyuki Gakkai Zasshi (Japan). 1999; 37(8):619-22.

21. Yoshida A, Matsumoto H, Iida Y, Takahashi T, Fujita Y, Tuji T, Fujikane T, Shimizu T, Ogasawara H, Saito Y. A case of chronic tubercu-lous pyothorax associated malignant lymphoma. Kekkaku (Japan). 1996; 71(6):415-21.

22. Taniguchi N, Fukuoka A, Amano I, Okamura H, Takenaka H, Morii T, Okamoto Y, Yoshikawa M, Konishi M, Tsukaguchi K, Hamada K, Yoneda T, Nariata N. A case of pleural malignant lymphoma associated with chronic tuberculous pyothorax. Kekkaku (Japan). 2002; 77(4):367-71

23. Mori N, Yatabe Y, Narita M, Kobayashi T, Asai J. Pyothorax-associated lymphoma. An unsusual case with biphenotypic character of T and B cells. Am J Surg Pathol. 1996;20(6):760-6.

Corresponding author:
Dr. Katrin Welcker
Department of Thoracic Surgery, Krankenhaus Großhansdorf, Zentrum für Pneumologie und Thoraxchirurgie, Wöhrendamm 80, 22927 Großhansdorf, Germany
drwelcker@t-online.de

Please cite as
Welcker K, Nakashima M, Diemel KD, Welker L, Galle J, Merz H, Branscheid D. Pyothorax-associated lymphoma (PAL): report and review of a rare entity. Thorac Surg Sci. 2004;1:Doc03.

This article is freely available from
http://www.egms.de/en/journals/tss/2004-1/tss000003.shtml

Published: *2004-10-01*