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Uncommon Late Relapse of Angioimmunoblastic T-Cell Lymphoma after 16-Year Remission Period

Edit Páyer · Zsófia Miltényi · Zsófia Simon · Lajos Szabados · Katalin Hegyi · Gábor Méhes · Árpád Illés

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Abbreviations

AITL	Angioimmunoblastic T-cell lymphoma
EBV	Epstein-Barr virus
^{18}FDG-PET/CT	^{18}Fluoro-deoxy-glucose Positron Emission Tomography/Computed Tomography
LDH	Lactate dehydrogenase
CHOP	Cyclophosphamide, doxorubicine, vincristine, prednisone
COPBLAM	Cyclophosphamide, vincristine, prednisone, bleomycin, adriamycin and procarbazin
CEVP	Cyclophosphamide, vinblastine, epirubicin and prednisone
DHAP	Dexamethasone, cytarabin, and cisplatin
TNF	Tumor necrosis factor
EBER	Epstein-Barr early RNA

Introduction

Angioimmunoblastic T-cell lymphoma is rare and aggressive disorder representing approximately 2% of all non-Hodgkin lyphomas [1], that affects mainly elderly patients [2]. Allergic reactions, infections and chemicals can all play role in the etiology [3], in most of the cases EBV genome can be detected in the environmental B-cells [4–6]. It is suggested that the EBV-related B-cell proliferation is secondary effect due to immunosupression [7].

Most patients present with fever, weight loss, lymphadenopathy, splenomegaly and skin rushes. Laboratory findings may include anaemia (often autoimmune hemolytic type), thrombocytopenia, elevated level of LDH and polyclonal hypergammaglobulinaemia [2]. Nevertheless, several autoimmune phenomena have been reported in association with AITL [8–15]. Characteristic histological features are effaced nodal architecture, increased vascular proliferation, dilated sinuses, and polymorphous T-cell infiltration with plasmacytes, macrophages, eosinophils and rarely Sternberg-Reed-like cells [16]. The neoplastic cells commonly express CD3, CD4, CD5, Bcl6, CD10 and CXCL13 on their surfaces [17–20].

Treatment usually includes anthracyclin based combinations, like CHOP. The clinical outcome of AITL may be varied with a median survival of less than 3 years and 5-year survival of around 30–35% [21–23]. The currently available staging systems and prognostic scores proved to be inadequate when applied to AITL cases [24]. Although a complete remission rate of 50% can be achieved with polychemotherapy, relapse rates still remain high [13]. Our patient's case is highly special as a 16-year-term complete remission and an association with B-cell lymphoma is reported. We would like to highlight the difficulties of treatment of AITL and the necessity of standardized therapeutic protocols.

Case Report

In 1990 a 53-year-old female patient presented with fever, skin rush and enlarged lymph nodes on the neck.

E. Páyer (✉) · Z. Miltényi · Z. Simon · Á. Illés
3rd Department of Internal Medicine, University of Debrecen, Medical and Health Science Center,
Móricz Zs. krt. 22,
4032 Debrecen, Hungary
e-mail: payeredit@vipmail.hu

L. Szabados
Scanomed Ltd,
Nagyerdei krt. 98,
Debrecen 4032, Hungary

K. Hegyi · G. Méhes
University of Debrecen, Medical and Health Science Center,
Institute of Pathology,
Nagyerdei krt. 98,
Debrecen 4032, Hungary

Histological analysis of lymph node biopsy diagnosed AITL (Fig. 1a, b, c). Six courses of CHOP chemotherapy were administered, and because of inadequate response in the abdominal region interferon-α was added to the treatment. However, no satisfactory response was realized, so rebiopsy was performed from the abdominal region. The result confirmed the initial diagnosis, therefore two courses of COPBLAM therapy was given, which was changed to CHOP because of serious respiratory distress syndrome and heart failure as side-effects of the chemotherapy. As a result, complete clinical remission was achieved by the end of 1991. There were no further important events in her follow-up until October 2007, when weakness, subfebrility and urticaria-like skin rushes appeared. Skin biopsy showed ANCA negative vasculitis, T-cell lymphoma could not be detected. Examinations did not prove either systemic autoimmun disorder or solid tumor. In April 2008, ^{18}FDG-PET/CT examination was performed which showed tracer enhancing lymph nodes in the abdomen (Fig. 2a). At that time, laboratory tests showed elevated levels of erythrocyte sedimentation rate, LDH, β2-microglobulin and hypogammaglobulinaemia. Laparoscopy was made to gain sample from the perihepatical lymph nodes, and histological analysis proved AITL again. Accordingly, CEVP therapy was started. After two cycles, interim ^{18}FDG-PET/CT showed complete metabolic remission. After the third course of CEVP therapy, she presented with swallowing difficulties. Therefore, an otolaryngeal examination was performed and a small piece of tissue was removed from the lower pharyngeal region. This lesion was diagnosed as lymphoplasmocytic lymphoma by the histologist (Fig. 1d, e, f). Altogether 6 courses of CEVP

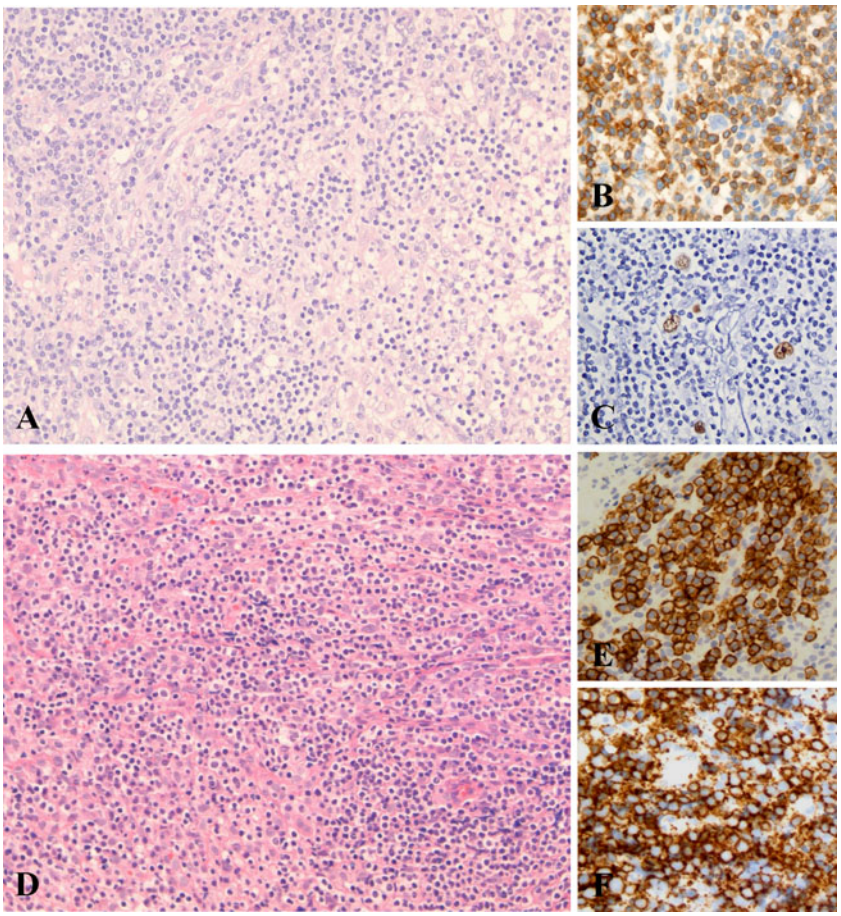

Fig. 1 Histological appearance of angioimmunoblastic T-cell lymphoma diagnosed in 1990 from a lymph node biopsy of the anterior neck region. Classical morphological changes included disorganized nodal architecture with irregular T-cell invasion, vessel proliferation and branching, as well as activated immunoblast-like cells by HE staining (**a**, 10× magnification). Most of the lymphocytes showed CD4 immunostaining, while atypical HRS-like large cells remained negative for T-cell markers (**b**, 20× magnification). This cell type proved to be positive for Epstein-Barr virus as demonstrated by EBER mRNA FISH on paraffin sections (**c**, 20× magnification). Identical morphology was stated in the lymph node biopsy taken 17 years later. An excision, made in 2008, from the pharyngeal mass causing swallowing difficulties resulted the diagnosis of small cell lymphoma with plasmocytic differentiation (lymphoplasmocytic lymphoma) due to the large masses of lymphoid and plasmocytic infiltrate (**d**, 10× magnification) expressing CD138 (**e**, 20× magnification) and CD20 (**f**, 20× magnification) by immunohistochemistry. A T-cell component and atypical large cells were absent in these sample

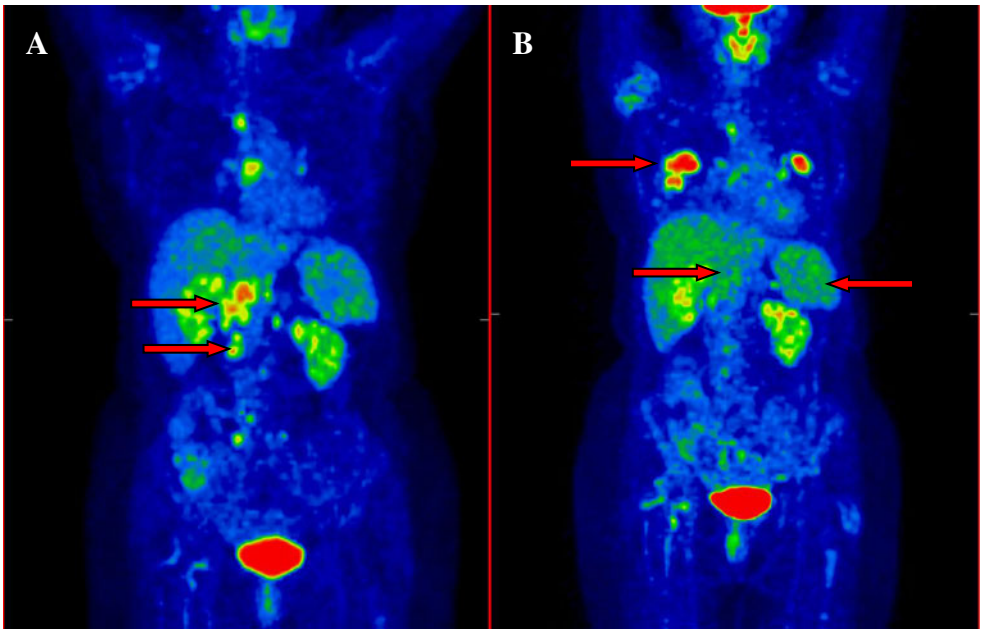

Fig. 2 ^{18}FDG-PET/CT was performed in 2008, when relapse occurred, showed increased metabolism in lymph nodes in the paraaortic region and in the hilum of the liver. SUV max. 5.02 (**a**, signed with *arrows*). High FDG uptake was proved by PET/CT in the lungs, spleen and hilum of the liver in 2009 (**b**, signed with *arrows*)

chemotherapy was given, then control ^{18}FDG-PET/CT showed complete metabolic remission. Nearly 1 year later she experienced fever and weakness. PET/CT suggested relapse both in the supra-, and infradiaphragmatic areas and splenic involvement, however there were no appropriate periferial lymph nodes for biopsy (Fig. 2b). Splenectomy and laparoscopic lymphadenectomy could not be performed due to the patient's generally failed condition. At least, DHAP chemotherapy with reduced doses was administered, which was discontinued because of renal failure caused by cisplatin. Afterwards, she received metyl-prednisolon monotherapy and abdominal involved field radiotherapy (36 Gy). No further progression could be recognized during the follow-up. However, she died of opportunistic infections and pancytopenia caused by the serious immuno- and myelosuppression at her home in August 2010, a year after the last chemotherapy, in spite of best supportive care. Autopsy showed lymphadenopathy in the abdominal region, splenomegaly, and diffuse mucosal bleeding. Histology of lymph nodes confirmed the AITL, but the spleen and the bone marrow were not examined.

Discussion

AITL is a rare disease with less than 3-year median overall survival and high relapse rates. Our case is unique with the 16-year remission period. This unusual behaviour and late appearance suggested that two separate disorders were diagnosed. Clonality analysis of the T-cell receptor gamma/delta genes was performed using the Biomed 2 primers which resulted in low quality PCR products not allowing the identification of the clonal relation between the 1990 and the 2008 samples. Further to sampling and aging problems especially in the archived sample from 1990, the highly heterogeneous composition and relatively low tumor cell fraction of AITL could be made responsible for the failure of the molecular analyses. Therefore, it was not possible to exclude that the AITL arising 16 years later was an unrelated second malignancy. AITL itself seems to be related to a substantial immune activation in the periferial blood and lymph nodes. The evidences for this include increased levels of serum solubile cytokins [25–28]. Recent studies have shown an increased expression of TNF receptor family member CD134 [29], chemokine receptor CXCR3 [30] and CD69, a marker of early T-cell activation [31]. These molecules are preferentially associated with T-helper(Th)-1 phenotype in normal T-cells, suggesting that Th-1 type differentiation characterised by IL-2 and interferon-γ production, is a feature of AITL [32]. Moreover, patients have shown defective T-cell responses supporting and underlying immunodeficiency. Abnormalities reported include reduction of absolute number of circulating T-cells, inverse CD4/CD8 ratio, high percentages of activated T-cells, defective T-cell response in vitro, and minimal helper and enhanced suppressor function [33, 34]. In our case, similar defects were not present, but decreased B-cell count was measured in contrast with reports [33]. Due to the immunosuppression caused by the defective immune response, infections and second tumors can evolve. In agreement with this, a lymphoplasmacytic lymphoma could be diagnosed in our patient. Based on data from other publications, B-cell lymphomas develop in about 10% of AITL cases [7]. Diffuse large B-cell lymphoma is the most frequent type, but no data could be found about lymphoplasmacytic lymphoma [35]. The ratio

of 10% may be underestimated considering the fact that repeated lymph node biopsies after diagnosis of AITL are rarely performed [35]. In most of the secondary developing lymphomas EBV genome can be detected which may be a result of the immunocomprised state [7]. Oligo- or polyclonal IgHv rearrangements have been shown by EBV-infected B-cells [4]. In our case an unambiguous lambda light chain monoclonality was detected and in situ hibridization for EBER mRNA was also positive (Fig. 1c). The clonal expansion and atypical somatic hypermutation of EBV positive B-cells can play a role in the development of B-cell lymphoma in AITL [4].

The treatment of relapses is complicated because of lacking standardized protocols. High dose chemotherapy followed by autologouos haemopoetic stem cell transplantation have been reported, but in our patient it did not come into question because of the age and comorbidities. Moreover, the toxicity caused by the previous treatments was significant, thus we tried to reduce the side-effects. Nevertheless, it is known that many patients die due to opportunistic infections which notes the narrow space between the effective chemotherapy and the resulting, potentially fatal infectious side-effects.

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