# A Case of EBER Positive Angioimmunoblastic T-cell Lymphoma Combined with Myxofibrosarcoma of the Pleura

Yasunobu SEKIGUCHI[*1], Ayataka ISHIKAWA[*2], Hiroaki KANDA[*2], Machiko KAWAMURA[*3], Shigeki TOMITA[*4] and Masaaki NOGUCHI[*5]

[*1]*Department of Hematology, Saitama Cancer Center*
[*2]*Department of Pathology, Saitama Cancer Center*
[*3]*Department of Clinical Laboratory Medicine, Saitama Cancer Center*
[*4]*Department of Pathology, Juntendo University Urayasu Hospital*
[*5]*Department of Hematology, Juntendo University Urayasu Hospital*

(Received September 13, 2021; Accepted November 2, 2021)

**A 76-year-man presented with generalized lymphadenopathy. Lymph node biopsy led to the diagnosis of Epstein-Barr virus-encoded small RNA in situ hybridization (EBER)-positive angioimmunoblastic T-cell lymphoma (AITL). He was initiated on treatment with oral prednisolone (PSL) at the dose of 50 mg/day; however, he was diagnosed as having right pleural effusion. He was started on treatment with cyclophosphamide, doxorubicin, vincristine and PSL (CHOP therapy). However, the right pleural effusion increased in size, and thoracentesis was performed. The aspirated pleural fluid was bloody, and since only a very small number of atypical cells were found, no definitive diagnosis could be made. CT revealed multiple nodular lesions in the pleura, and thoracoscopy was performed, which revealed jelly-like white lesions in the right parietal pleura. Biopsy raised the suspicion of undifferentiated pleomorphic sarcoma (UPS). Treatment with carboplatin and pemetrexed was started, but his respiratory symptoms worsened and he died. Autopsy revealed evidence of complete remission of AITL and myxofibrosarcoma (MFS) of the pleura. This is the first reported case of AITL combined with MFS.**

**Key words: angioimmunoblastic T-cell lymphoma, myxofibrosarcoma, immunodeficiency, EBER, second primary malignancy**

## INTRODUCTION

Angioimmunoblastic T-cell lymphoma (AITL) is known to be associated with immunodeficiency [1–8]. As second primary malignancies thought to be caused by the immunodeficiency in cases of AITL, Epstein-Barr virus-encoded small RNA in situ hybridization (EBER)-positive or -negative lymphoma and lymphoproliferative disorder (LPD) have been reported [2, 3, 9–11]. The only reported case of malignancy other than lymphoma and LPD is squamous cell carcinoma [4]. Therefore, the details of the course and prognosis of AITL patients with second primary malignancies other than lymphoma and LPD are unknown. Our present case diagnosed as having AITL combined with myxofibrosarcoma (MFS) had atypical clinical features, suggestive of a poor prognosis.

## CASE REPORT

The patient, a 76-year-old male, had a history of hypertension, and no significant family history. Fig. 1 shows his clinical course.

In the first; from the onset of AITL to make the diagnosis as AITL: Three weeks before consultation, he noticed bilateral cervical and right inguinal lymphadenopathy, and visited Juntendo University Urayasu Hospital (on day 1 of consultation). Table 1 shows the hematological findings, which revealed elevated serum levels of lactate dehydrogenase (LDH) and soluble interleukin-2 receptor (sIL-2R). Body computed tomography (CT) revealed lymphadenopathy of multiple lymph node groups, including the bilateral cervical, mediastinal, bilateral axillary, and para-aortic lymph nodes (Fig. 2A–D). No abnormalities were found in the lung or pleura (Fig. 3A). We did not carry out positron emission tomography-computed tomography (PET-CT). Cervical lymph node biopsy was performed. Hematoxylin-and-eosin (HE) staining showed medium-sized atypical cells with clear cytoplasm, vascularity, and eosinophil infiltration (Fig. 4A). Immunohistochemistry showed positive staining for cluster of differentiation (CD) [3–5, 7, 21], programmed cell death 1 (PD-1), and EBER, and negative staining for CD [8, 10], T-cell intracellular antigen (TIA), immunoglobulin A (IgA), $\kappa$, and $\lambda$ (Fig. 4B–N). Based on the findings, he was diagnosed as having AITL. There was no evidence of invasion of the bone marrow or central nervous system. he was classified as having clinical stage III AITL according to the Ann Arbor classification, and he had no B symptoms. His performance status (PS) was 1. His international prognostic index (IPI) was high-intermediate (HI) (age,

Yasunobu SEKIGUCHI, Department of Hematology, Saitama Cancer Center, 780 Komuro, Ina, Kita-adachi-gun, Saitama 362-0806, Japan
Tel: +81-48-722-1111 Fax: +81-48-723-5197 E-mail: yasu_sek@saitama-pho.jp

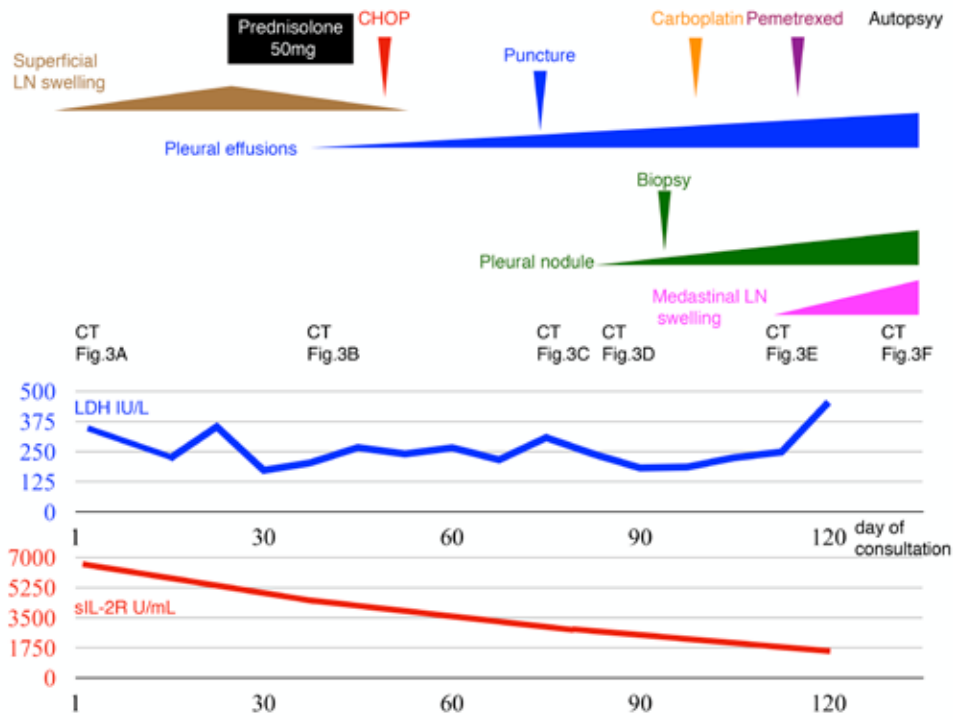


**Fig. 1** Clinical course

**Table 1** Laboratory findings at the first visit (on day 1 of consultation)

| CBC | | Biochemistry | | Tumor marker | |
|---|---|---|---|---|---|
| WBC | 13,100 /μL | T.P | 7.1 g/dL | sIL-2R | 6,080 U/mL |
| Band | 6.0% | Alb | 3.4 g/dL | CEA | 11.5 ng/mL |
| Seg | 61.5% | BUN | 30 mg/dL | CA19-9 | 9.0 U/mL |
| Ly | 18.5% | Cr | 1.55 mg/dlL | | |
| Mono | 9.5% | T-Bil | 0.3 mg/dL | | |
| Eo | 3.5% | AST | 46 IU/L | | |
| Ba | 1.0% | ALT | 29 IU/L | Immuno-Serological findings | |
| RBC | 402 × $10^4$ /μL | LDH | 334 IU/L | HTVL-I Ab | negative |
| Hb | 13.2 g/dL | ALP | 307 IU/L | HIV Ab | negative |
| Hct | 42.5% | AMY | 50 IU/L | HBsAg | negative |
| MCV | 105.7 fL | γ-GTP | 64 IU/L | HBsAb | negative |
| MCH | 32.9 pg | T-CHO | 162 mg/dL | HBcAb | negative |
| PLT | 26.4 × $10^4$ /μL | BS | 104 mg/dL | HCVAb | negative |
| | | CRP | 0.8 mg/dL | IgG | 1332 mg/dL |
| Cogulation | | | | IgA | 642 mg/dL |
| PT | 100% | Urine | | IgM | 114 mg/dL |
| APTT | 26.1 sec | Normal | | ANA | < 40 times |

Abbreviation; WBC, white blood cells; Band, band cell; Seg, segmented cell; Ly, lymphocyte; Mono, monocyte; Eo, eosinophil; Ba, basophil; RBC, red blood cell; Hb, hemoglobin; Hct, hematocrit; MCV, mean corpuscular volume; MCH, mean corpuscular hemoglobin; PlT, platelet; PT, prothrombin time; APTT, activated partial thromboplastin time; T.P, total protein; Alb, albumin; BUN, blood urea nitrogen; Cr, creatine; T-BIL, total-bilirubin; AST, aminotransferase; ALT, alanine aminotransferase; LDH, lactate dehydrogenase; ALP, alkaline phosphatase; AMY, amylase; γ-GTP, γ-guanosine triphosphate; T-CHO, total cholesterol; BS, blood sugar; CRP, C-reactive protein; sIL-2R, soluble interleukin-2 receptor; CEA, carcinoembryonic antigen; CA19-9, carbohydrate antigen 19-9; HTLV-1 Ab, human T-cell leukemia virus type 1 antibody; HIV Ab, human immunodeficiency virus antibody: HBsAg, hepatitis B virus antigen; HBsAb, hepatitis B virus antibody; HBcAb, hepatitis B virus core antibody; HCV Ab, hepatitis C virus antibody; IgG, immunoglobulin G; IgA, immunoglobulin A; IgM, immunoglobulin M; ANA, antinuclear antibody

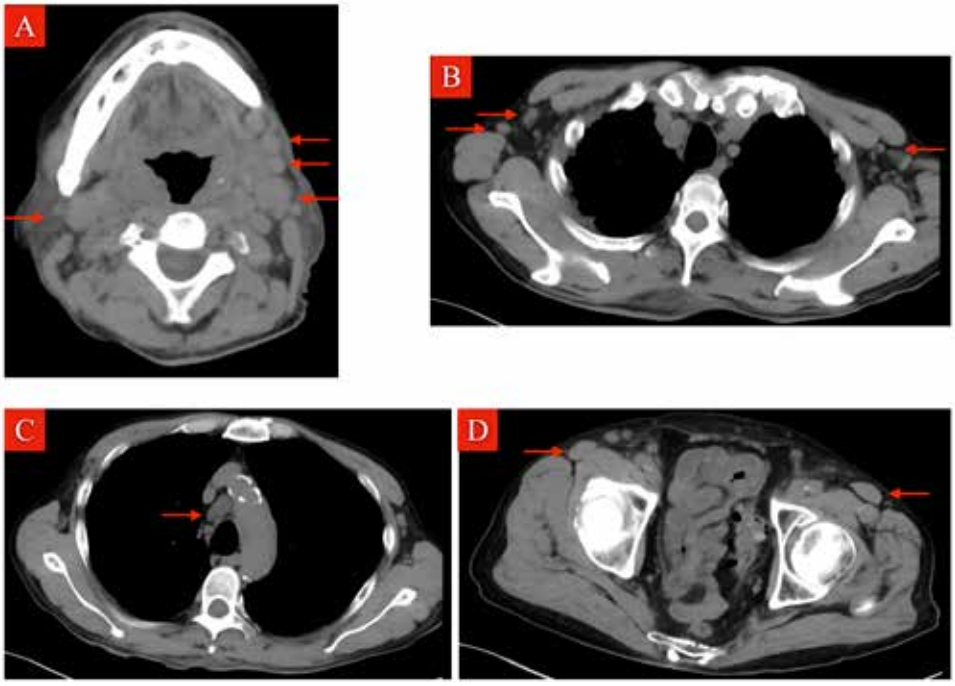


**Fig. 2** Whole-body CT findings at the first visit (on day 1 of consultation)
A: Bilateral cervical lymphadenopathy (red arrows).
B: Bilateral axillary lymphadenopathy (red arrows).
C: Mediastinal lymphadenopathy (red arrow).
D: Bilateral inguinal lymphadenopathy (red arrows).

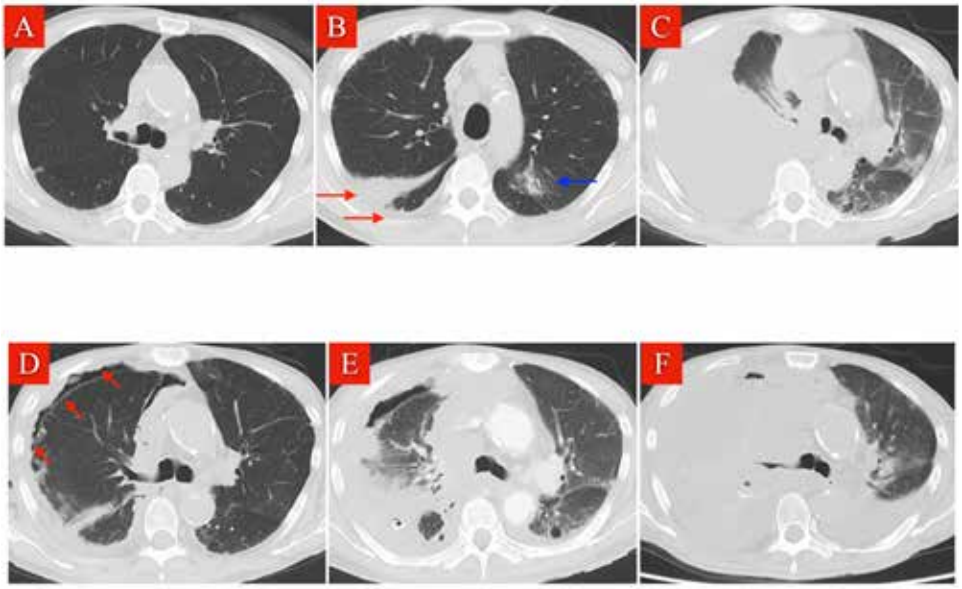


**Fig. 3** Lung CT
A: There were no abnormalities in the lung or pleura. (on day 1)
B: Right pleural effusion, interlobar effusion (red arrows) and left pneumonia (blue arrow) are seen. (on day 45)
C: The right pleural effusion has increased in size. (on day 86)
D: Multiple nodular lesions are observed in the right pleura (red arrows). (on day 90)
E: The right pleural effusion worsened after treatment with carboplatin. (on day 118)
F: The right pleural effusion worsened further after treatment with pemetrexed. (on day 137)

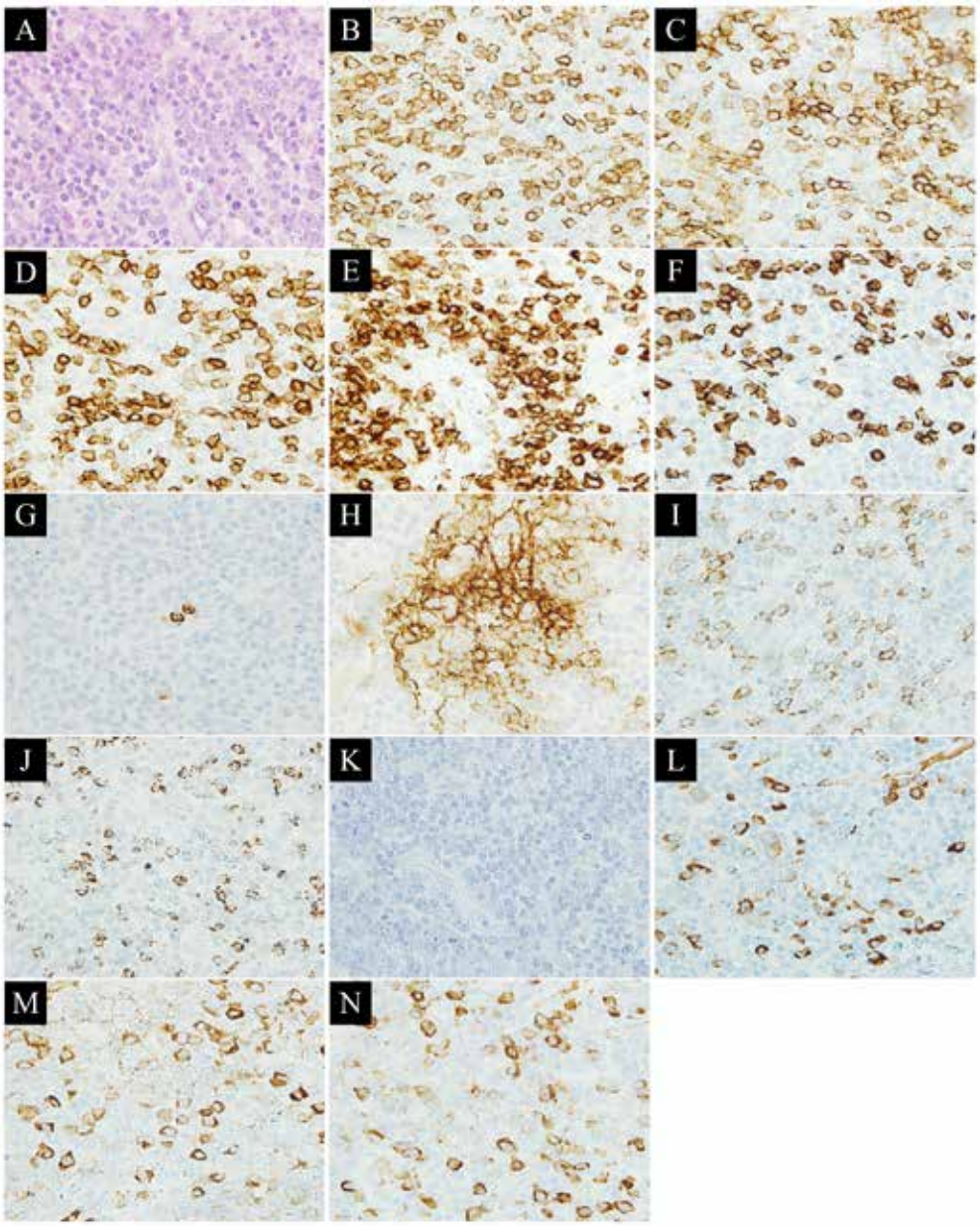


**Fig. 4** Lymph node biopsy (×400 ) (on day 12)
A: HE staining; Medium-sized atypical cells with clear cytoplasm are observed. Vascularity and eosinophil infiltration are also seen.
B: CD3 staining: positive
C: CD4 staining: positive
D: CD5 staining: positive
E: CD7 staining: positive
F: CD8 staining: negative
G: CD10 staining: negative
H: CD21 staining: positive, with proliferation of follicular dendritic cells (FDC)
I: PD-1 staining: focally positive
J: TIA-1 staining: negative
K: EBER staining: some positive cells
L: IgA staining: negative
M: $\kappa$ staining: negative
N: $\lambda$ staining: negative

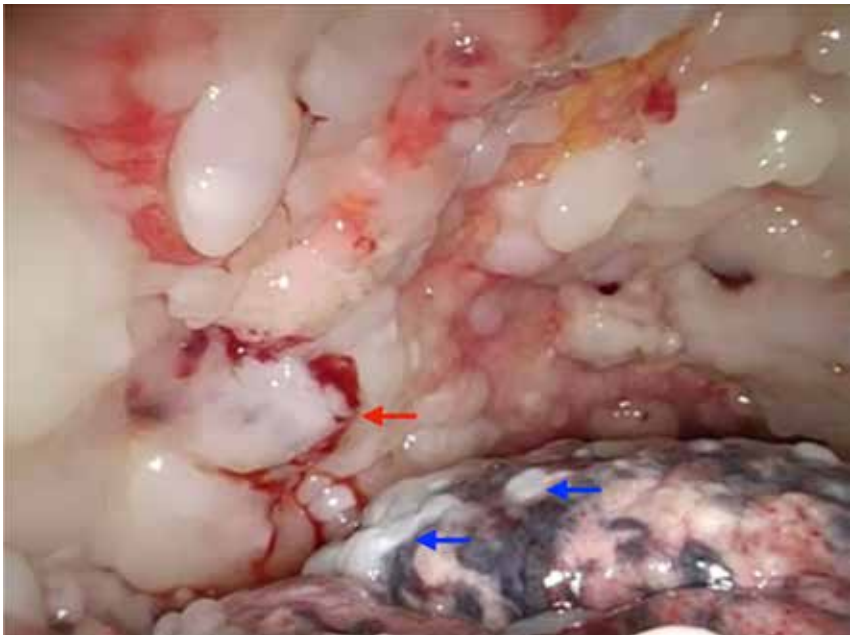

**Fig. 5** Gross thoracoscopic findings (on day 91)
Multiple jelly-like white lesions were seen in the right parietal pleura. Biopsy specimens were obtained from the lesions (red arrow). White lesions were also observed on the lung surface (blue arrows).

LDH, stage), and his Prognostic Index for peripheral T-cell lymphoma unspecified (PTCL-U) (PIT) was Group 3 (age, LDH). The lymphadenopathy worsened, and he was initiated on treatment with oral prednisolone (PSL) at 50 mg/day on day 23 (because no definitive diagnosis was obtained at that time). A definitive diagnosis was obtained on day 45.

In the second; treatment for AITL: His respiratory symptoms worsened, and CT revealed right pleural effusion and interlobar effusion (Fig. 3B) (on day 45). The CT images also showed opacities suggestive of pneumonia in the left lung (Fig. 3B) (on day 45). The results of sputum culture, including for mycobacteria, serum tests for $\beta$-D glucan and *Aspergillus* antigen, and the T-SPOT were negative. The pleural effusion was considered as being the result of progression of AITL, and the patient was started on treatment with cyclophosphamide, doxorubicin, vincristine and PSL (CHOP therapy) on day 57. His clinical symptoms did not improve, and CT was performed. The right pleural effusion had increased in size (Fig. 3C)(on day86).

In the third; from clinical symptoms got worse: Thoracentesis was performed on day 87. The aspirated fluid was bloody, and as only a small number of atypical cells were seen, no definitive diagnosis could be made. Chromosomal analysis (G-banding) revealed a normal karyotype. Cultures were negative. CT performed immediately after thoracentesis revealed multiple nodular lesions in the right pleura (Fig. 3D)(on day 90). The mediastinal lymphadenopathy had decreased. Pleural malignancy was suspected, and thoracoscopy was performed on day 91, which revealed jelly-like white lesions in the right parietal pleura. Biopsy specimens were obtained from the lesions (Fig. 5, red arrow). White lesions were also observed on the lung surface (Fig. 5, blue arrows). The histopathological findings were unclear due to insufficient material, but raised the suspicion of undifferentiated pleomorphic sarcoma (UPS) (data not shown). Peripheral blood examination revealed positive results for 5 cytomegalovirus (CMV) pp65 antigens (C7-horseradish peroxidase [HRP]). Treatment with carboplatin was started on day 112 and pemetrexed was started on day 119, but the right pleural effusion worsened further (Fig. 3E, F) (on day 118 and 137). The respiratory symptoms also worsened, and the patient died on day 142.

In the fourth; Autopsy: Autopsy was performed, which revealed evidence of complete remission (CR) of AITL. The histopathological findings of the pleural lesions are shown (Fig. 6). HE staining showed proliferating spindle-shaped or giant atypical cells in a background of myxomatous stroma (Fig. 6A). Mitoses were observed (Fig. 6B). Alcian blue-periodic acid-Schiff (PAS)-double staining was positive (Fig. 6C), epithelial membrane antigen (EMA) staining was positive in some cells (Fig. 6D), Ki67 staining was positive in 25% of the cells (Fig. 6E), and immunohistochemistry revealed positive staining of some cells for smooth muscle actin (SMA) (Fig. 6F), and positive staining for vimentin (Fig. 6G). The results also showed negative staining for anion exchanger 1 (AE1)/AE3, CD34, S-100, desmin, calretinin, podoplanin (D2−40), human melanoma black 45 (HMB45), c-kit, and integrase interactor 1 (INI-1) (data not shown). Based on the above findings, the patient was diagnosed as having MFS. The French Federation of Cancer Centers Sarcoma Group (FNCLCC) grade was score 7 (high grade) [12]. Evidence of mediastinal invasion by the MFS was also found.

## DISCUSSION

At the time that he was diagnosed as having AITL, no pleural effusion or pleural nodules were observed (Fig. 3A), suggesting that the MFS developed at the time when pleural effusion was detected, approximately 2 months after the onset of AITL (Fig. 3B)(on day

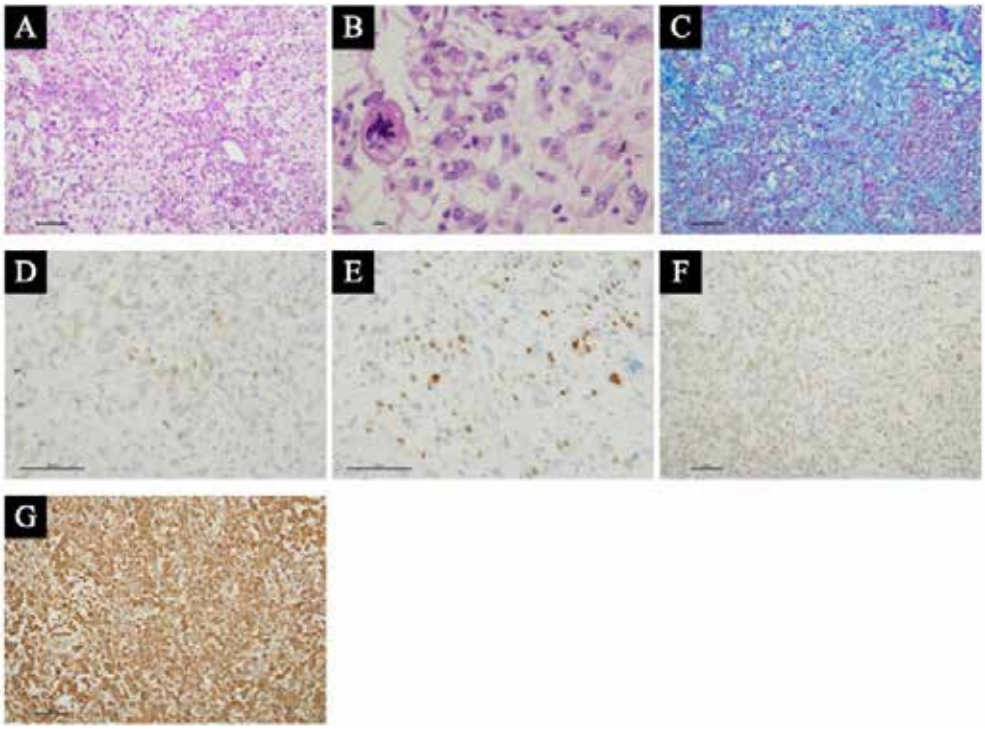


**Fig. 6** Pleural biopsy findings at autopsy (on day 142)
A: HE staining: Proliferating spindle-shaped or giant atypical cells in a background of myxomatous stroma.
B: HE staining: Mitoses are prominent.
C: Alcian blue-PAS double staining: positive
D: EMA staining: positive in some cells
E: Ki67 staining: positive in 25% of cells
F: SMA staining: positive in some cells
G: Vimentin staining: positive

**Table 2** Reports on immunodeficiency associated with myxofibrosarcoma

| | age(y)/sex | BD | BD treatment | BD outcome | interval from BD to MFS | MFS onset site | MFS treatment | MFS outcome | final outcome | cause of death | reference |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 33/M | ML<br>AD | CHOP<br>HD-VP16<br>CHASE<br>Auto<br>Steroid | remission | 11m | liver | Excision | no relapse for 2y | survival | – | 13 |
| 2 | 43/n.a | RF<br>HT | KT<br>mPSL<br>CsA<br>CD3抗体<br>AZT | n.a | 6y | right neck | Excision | no relapse | survival | – | 14 |
| 3 | n.a | n.a | BMT | n.a | n.a | liver | n.a | n.a | n.a | n.a | 15 |
| 4 | n.a | n.a | BMT | n.a | n.a | liver | n.a | n.a | n.a | n.a | 15 |
| 5 | 76/M | EBER+AITL<br>CMV | PSL<br>CHOP | CR | 2m | Pleura | Carboplatin<br>Pemetrexed | PD | death | MFS | this case |

Abbreviation; y, years; BD, basal disease; MFS, myxofibrosarcoma; M, man; n.a,not available; ML, malignant lymphoma; AD, Atopic dermatitis; RF, renal failure; HT, hypertension; EBER, Epstein Barr virus encoded RNA; AITL, angioimmunoblastic lymphma; CMV, Cytomegalovirus; CHOP, cyclophosphamide, doxorubicin, vincri stine and prednisone; HD-VP16, high dose etoposide; CHASE, CPA, Cytarabine, DEX, Dexamethasone,etoposide; Auto, autotransplant; KT, kidney transplant; mPSL, methylprednisolone; CsA, Ciclospolin; Ab, antibody; AZT, azathioprine; BMT, bone marrow transplant; PSL, prednisolone; CR, complete remission; m, months; PD, progression disease

45). In addition, when the pleural nodular lesions were detected, there were no mediastinal lesions (Fig. 3D)(on day 90), suggesting that the pleura was the primary site of the MFS. Mediastinal invasion was considered to have occurred even later. He was refractory to chemotherapy, and the disease progressed rapidly, resulting in early death. Autopsy revealed evidence of CR of the AITL, suggesting that He died of respiratory failure caused by the MFS.

AITL is known to be associated with immunodeficiency [1–8]. The patient reported herein was positive for EBER and CMV (C7-HRP), suggesting an association with immunodeficiency.

As second primary malignancies thought to be caused by immunodeficiency in cases of AITL, EBER-positive or -negative lymphoma and LPD have been reported [2, 3, 9–11]. To the best of our knowledge, the only reported case of malignancy other than lymphoma and LPD is squamous cell carcinoma [4]. Therefore, the details of the pathogenetic mechanisms, incidence, and prognosis of second primary malignancies other than lymphoma or LPD in patients with AITL remain unclear. In addition, there have been no reports of MFS combined with AITL.

On the other hand, 4 cases of MFS in immunodeficiency states have been reported previously (Table 2). In all the 4 cases, the MFS developed after organ transplantation: after autologous hematopoietic stem cell transplantation in 1 case, after kidney transplantation in 1 case, and after allogeneic bone marrow transplantation in 2 cases. Two patients whose prognoses were known (cases 1 and 2) were confirmed to be alive, and both of them had undergone surgical resection of the MFS. Since the only known curative treatment for MFS is surgical resection [16], it is considered that the surgical resection would lead to an improved prognosis.

Surgical resection could not be performed in him reported herein, because thoracoscopic biopsy failed to yield a definitive diagnosis and the disease progressed rapidly. Failure to perform surgical resection may have led to the poor prognosis. If a patient with AITL is diagnosed as having pleural effusion of unknown origin, a high index of suspicion must be borne for MFS and detailed examination must be performed immediately. Magnetic resonance imaging (MRI) has been reported to be useful in diagnostic imaging of MFS [16]. We think that MRI should be performed as early as possible.

In regard to the sites of onset of MFS, MFS develops in the dermis or subcutis in approximately two-thirds of the cases [17]. The limbs are the most common sites, followed by the trunk and the head and neck region [16]. MFS develops in the fascia or skeletal muscle in approximately one-third of cases [17]. However, there have been only two previous cases of pleural lesions, as in the present case [18, 19]. In addition, when MFS develops in the deeper parts, the lesions are often poorly defined and uninodular [17]. Furthermore, MFS has been reported to show invasive growth [16]. The present case was atypical, in that there were pleural lesions (Fig. 3D) and multiple well-defined nodules even though the lesions were deep (Fig. 5).

Usually, MFS progresses slowly [16]. However, in the present case, the progression was rapid, with death resulting in approximately 3 months after the onset. The clinical course was also atypical. Chemotherapy-induced immunosuppression was speculated to be involved in the rapid progression of MFS.

In fact, Sendo *et al.* reported that MFS of the liver developed after autologous transplantation for malignant lymphoma and progressed rapidly despite the low-grade malignancy [13]. They pointed out that immunodeficiency may have been involved in the rapid progression [13]. In addition, there have been only 3 reported cases of MFS of the liver [13, 15], in all of which MFS developed after hematopoietic stem cell transplantation [13, 15]. In all the 3 cases, the condition was thought to be a second primary malignancy precipitated by immunodeficiency [13, 15]. It has been suggested that MFS developing in patients with immunodeficiency states is associated with atypical clinical features.

In conclusion, we encountered a case of MFS with a poor prognosis in a patient with AITL, that was considered to be precipitated by AITL-associated immunodeficiency. This is the first reported case of MFS combined with AITL. It was considered that chemotherapy-induced immunosuppression led to the rapid progression of MFS in our patient. It should be noted that MFS arising in immunodeficiency states may be associated with atypical clinical features. We think that in AITL cases, careful attention should be paid to the possible development of second primary malignancies [4]. But we cannot deny possibility of accidental double cancer.

**REFERENCES**


1) Eminger LA, Hall LD, Hesterman KS, Heymann WR. Epstein-Barr virus: dermatologic associations and implications: part II. Associated lymphoproliferative disorders and solid tumors. J Am Acad Dermatol. 2015; 72: 21–34.
2) Smeltzer JP, Viswanatha DS, Habermann TM, Patnaik MM. Secondary Epstein-Barr virus associated lymphoproliferative disorder developing in a patient with angioimmunoblastic T cell lymphoma on vorinostat. Am J Hematol. 2012; 87: 927–8.
3) Yang QX, Pei XJ, Tian PX, Yang Li, Zhi Li. Secondary cutaneous Epstein-Barr virus-associated diffuse large B-cell lymphoma in a patient with angioimmunoblastic T-cell lymphoma: a case report and review of literature. Diagn Pathol 2012; 7: 7.
4) Habermann W, Anderhuber W, Humer-Fuchs U, Stammberger H. Simultaneous occurrence of metastatic tonsillar squamous cell carcinoma and angioimmunoblastic T-cell lymphoma in a cervical lymph node. J Laryngol Otol. 1997; 111: 580–2.
5) Castillo JJ, Sinclair N, Stachurski D, Jacobsen ED. Positive HIV ELISA test, autoimmune hemolytic anemia, and generalized lymphadenopathy: a unifying diagnosis.Am J Hematol. 2011 Aug; 86(8): 690–3.
6) Castillo JJ, Beltran BE, Bibas M, Bower M, Collins JA, Cwynarski K, *et al.* Prognostic factors in patients with HIV-associated peripheral T-cell lymphoma: a multicenter study. Am J Hematol. 2011; 86: 256–61.
7) Dogan A, Attygalle AD, Kyriakou C. Angioimmunoblastic T-cell lymphoma. Br J Haematol. 2003; 121: 681–91.
8) de Leval L, Gisselbrecht C, Gaulard P. Advances in the understanding and management of angioimmunoblastic T-cell lymphoma.Br J Haematol. 2010 Mar; 148(5): 673–89.
9) Hawley RC, Cankovic M, Zarbo RJ. Angioimmunoblastic T-cell lymphoma with supervening Epstein-Barr virus-associated large B-cell lymphoma. Arch Pathol Lab Med. 2006 Nov; 130(11): 1707–11.
10) Jiang M, Bennani NN, Feldman AL. Expert Rev Hematol. Lymphoma classification update: T-cell lymphomas, Hodgkin lymphomas, and histiocytic/dendritic cell neoplasms 2017; 10:

239–249.
11) Tan BT, Warnke RA, Arber DA. The frequency of B- and T-cell gene rearrangements and epstein-barr virus in T-cell lymphomas: a comparison between angioimmunoblastic T-cell lymphoma and peripheral T-cell lymphoma, unspecified with and without associated B-cell proliferations. J Mol Diagn. 2006; 8: 466–75.
12) Neuville A, Chibon F, Coindre JM. Grading of soft tissue sarcomas: from histological to molecular assessment. Pathology. 2014; 46: 113–20.
13) Sendo H, Kanaji S, Niwa H, Oshikiri T, Kominami H,Kawasaki K, *et al*. A case of a low grade myxofibrosarcoma of the liver which increased rapidly. Jpn J Gastroenterol Surg. 2013; 46: 494–501.
14) C P Soper, P A Andrews, M R Bending, L Singh, C Fisher. Cervical myxofibrosarcoma in a renal allograft recipient treated with murine anti-CD3 monoclonal antibody therapy. Nephrol Dial Transplant. 1998; 13: 1902–3.
15) Curtis RE, Rowlings PA, Deeg HJ, Shriner DA, Socíe G, Travis LB, *et al*. Solid cancers after bone marrow transplantation. N Engl J Med. 1997 Mar 27; 336(13): 897–904.
16) Roland CL, Wang WL, Lazar AJ, Torres KE. Myxofibrosarcoma. Surg Oncol Clin N Am. 2016; 25: 775–88.
17) Fujimoto N, Fujii N, Uenishi T, Tanaka T. A case of myxofibrosarcoma. Skin Cancer. 2008; 23: 175–179.
18) Neagu TP, Sinescu RD, Enache V, Achim SC, Ţigliş M, Mirea LE. Metastatic high-grade myxofibrosarcoma: review of a clinical case. Rom J Morphol Embryol. 2017; 58: 603–609.
19) Hambleton C, Noureldine S, Gill F, Moroz K, Kandil E. Myxofibrosarcoma with metastasis to the lungs, pleura, and mediastinum: a case report and review of literature. Int J Clin Exp Med. 2012; 5: 92–5.