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CASE REPORT

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A case of lymphomatous pleural effusion from angioimmunoblastic T-cell lymphoma: The methodology of cell transfer technique and immunocytochemistry on an inadequate cytology specimen can potentially guide us to the correct diagnosis

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1 | INTRODUCTION

Angioimmunoblastic T-cell lymphoma (AITL), a diverse, but aggressive haematopoietic neoplasm of mature follicular helper T-cells, might be occasionally complicated with serous effusions.[1,2] However, lymphomatous effusion caused by AITL, accounting only for less than 1% of all malignant effusions due to haematopoietic diseases, has been very rarely reported, because of the difficulty on cytological diagnosis.[1–5] Malignant effusion of AITL often poses a diagnostically severe challenge to not only haematologists but cytopathologists, since it is very hard to obtain the specific cytological findings, and its presence and is difficult to diagnose preoperatively.[2,3] Furthermore, there has been a description of a patient with AITL presenting first with developing bilateral pleural effusions, followed by systemic lymphadenopathies.[6] In these contexts, early accurate diagnosis and a regimen of radical chemotherapy treatment might be able to improve the survival rates of AITL patients.

We report a case of AITL in which a complicated effusion was recognised first, and the cytological diagnosis was very difficult due to the insufficient/inadequate volume of submitted pleural effusion. However, the methodology of cell transfer technique and immunocytochemistry could have most likely guided us to the correct cytological diagnosis.

2 | CASE PRESENTATION

An 84-year-old female presented with a chief complaint of exertional dyspnoea, due to progressive bilateral pleural effusions detected by ambulatory chest X-ray. She had an unremarkable medical history. A subsequent chest computed tomography (CT) scan incidentally revealed overt lymphadenopathy in the right hilar and mediastinal regions, together with bilateral pleural effusions. In addition, many cervical and intraperitoneal swollen and fused lymph nodes were generally identified on neck/abdominal CT, which prompted a thorough examination. The patient's laboratory studies showed variable inflammatory reactions: lactate dehydrogenase, 255 U/L; C-reactive protein, 1.54 mg/dL; and white blood cell count, 11,400/mm^3. Her tumour marker, serum soluble interleukin 2 receptor, was significantly increased up to 4015 U/mL.

The patient was first referred to the Department of Respiratory Medicine, where malignant lymphoma had not been suspected prior

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to thorough examination including CT scan or lymph node biopsy. Therefore, clinicians submitted a small volume, only 10 mL, of yellowish and turbid pleural effusion for cytological examination. At low to high magnification, its aspiration cytology showed small to rarely medium-to-large, round to ovoid lymphocytes having occasionally prominent nucleoli (Figure 1A,B), admixed with a very small number of atypical plasmacytoid cells (Figure 1A) and immature enlarged lymphoid cells (Figure 1B). The background revealed variable proportions of inflammatory cells, including neutrophils, eosinophils, histiocytes, and plasma cells (Figure 1A,B), or scattered mesothelial cells. May-Grünwald-Giemsa stain identified a small number of enlarged blastoid lymphoid cells having irregularly shaped nuclei and basophilic cytoplasm (Figure 1B). Mitosis was very rarely seen. There were no apparent apoptotic cells, Hodgkin/Reed-Sternberg cells, or atypical irregular lymphocytes having clear to pale cytoplasm. Cytology of the pleural effusion initially diagnosed as likely suspicious for a few neoplastic lymphocytes, not further specified, in which it was very hard to conclude the status as benign or malignant. The cytological differential diagnoses included reactive inflammation (i.e., pleuritis), AITL, or plasmacytoma. We performed a careful cytological and immunocytochemical re-examination with regard to the atypical immature enlarged lymphoid cells. By using a cell transfer method,[7] the atypical large, round to ovoid lymphocytes were specifically immunopositive for CD3 and CD5 (Figure 1C,D). Additional immunocytochemistry was not performed due to the insufficient/inadequate amount of submitted specimen.

Subsequently, a biopsy of the swollen inguinal lymph node was performed. Under low-power view, the enlarged lymph node revealed complete loss of follicles with focal extra-nodal involvements of neoplastic cells (Figure 2A). The high-power view showed a diffuse proliferation of overtly atypical medium-to-large lymphoid cells having characteristically abundant clear cytoplasm, admixed with a number of swollen high endothelial venules, and scattered eosinophils or plasma cells (Figure 2B). These aggregated atypical lymphoid cells were surrounding the high endothelial venules (Figure 2B). Mitosis was readily seen. On immunohistochemistry, the tumour cells were overtly positive for CD3/5/4 (Figure 2C–E) and weakly positive for bcl-6, programmed death receptor-1 (PD-1) (Figure 2F,G) and CD10, whereas they were negative for CD20. Moreover, the CD23-immunopositive follicular dendritic cell meshwork was irregularly

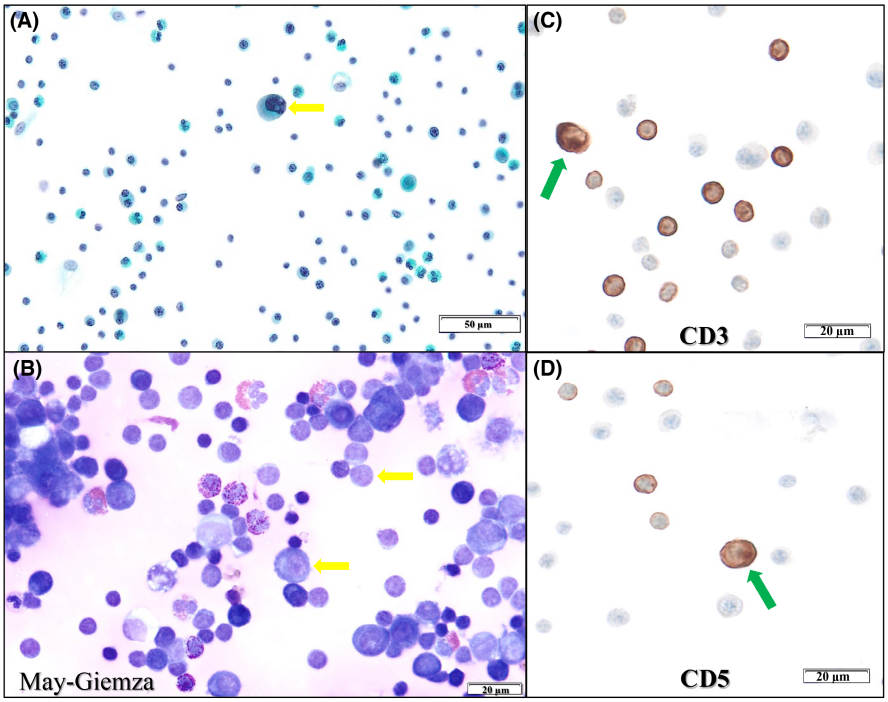

FIGURE 1 The cytomorphological/immunocytochemical findings on aspirated pleural effusion specimens. (A) Clinicians submitted a small volume, only 10 mL, of yellowish and turbid pleural effusion for cytological examination. The background revealed variable proportions of inflammatory cells, including neutrophils, eosinophils, histiocytes, and plasma cells, or scattered mesothelial cells. Atypical plasmacytoid cells having an irregularly enlarged nucleus (arrow) were very rarely seen (direct smear, Papanicolaou staining, ×400; scale bar = 50 μm). (B) May-Grünwald-Giemsa stain showed small to rarely medium-to-large, round to ovoid lymphocytes having occasionally prominent nucleoli, admixed with a very small number of immature enlarged lymphoid cells (arrows). These blastoid cells contained irregular-shaped nuclei and basophilic cytoplasm. There were no apparent apoptotic cells, Hodgkin/Reed-Sternberg cells, or atypical irregular lymphocytes having clear to pale cytoplasm (direct smear, May-Grünwald-Giemsa staining, ×1000; scale bar = 20 μm). (C,D) We performed a careful immunocytochemical re-examination with regard to the atypical immature enlarged lymphoid cells. By using a cell transfer method, the atypical large, round to ovoid lymphocytes (arrows)were specifically immunopositive for CD3 (C) and CD5 (D). Additional immunocytochemistry was not examined due to the insufficient/inadequate amount of the submitted specimen (immunocytochemistry, ×1000; scale bars = 20 μm).

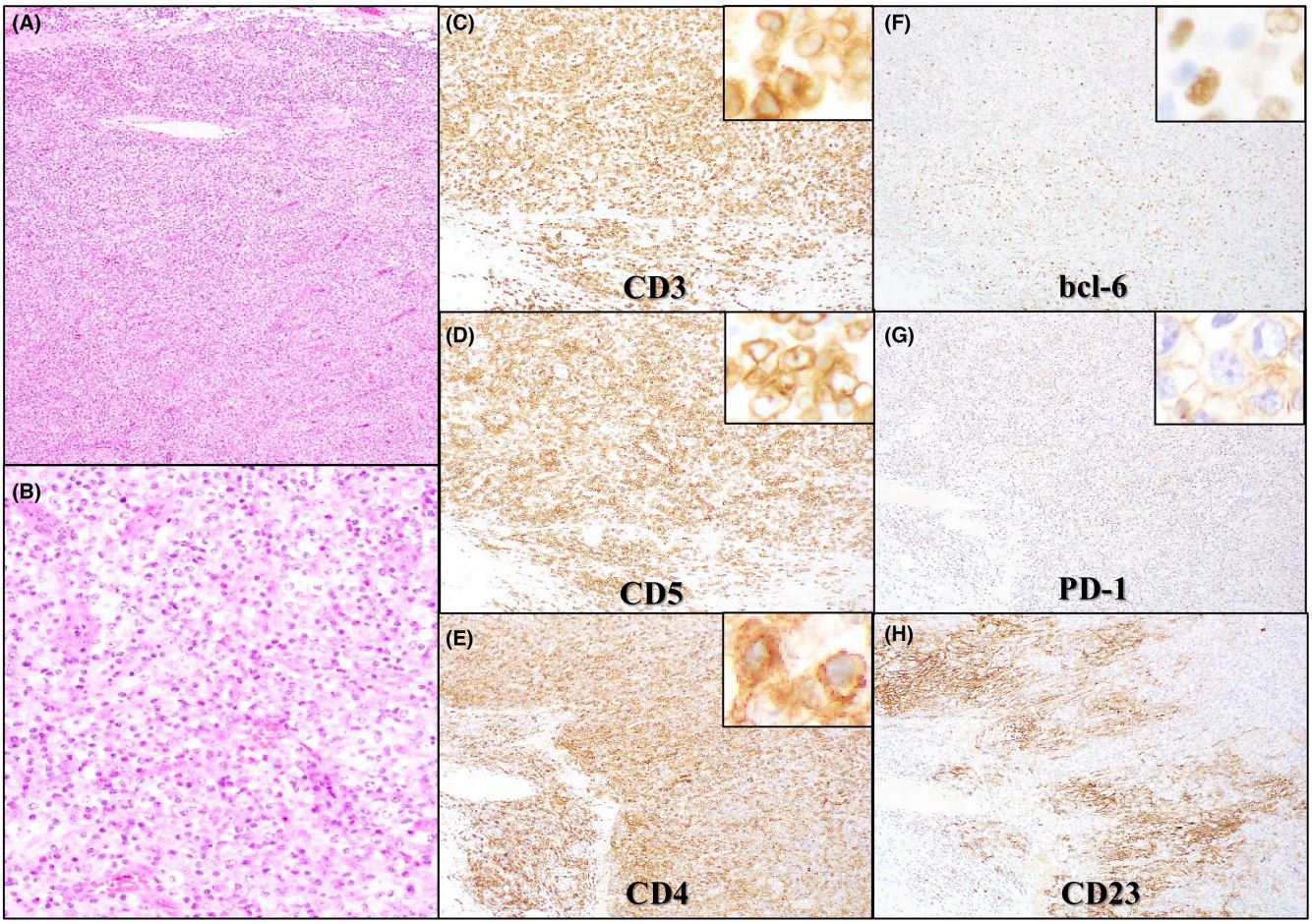

FIGURE 2 The histological/immunohistochemical findings on the tissue of swollen inguinal lymph node. (A) Under low-power view, the enlarged lymph node revealed complete loss of follicles with focal extra-nodal involvements of neoplastic cells (H&E staining, ×40). (B) The high-power view showed a diffuse proliferation of overtly atypical medium-to-large lymphoid cells having characteristically abundant clear cytoplasm, admixed with a number of swollen high endothelial venules, and scattered eosinophils or plasma cells. These aggregated atypical lymphoid cells were surrounding the high endothelial venules (H&E staining, ×200). (C-H) On immunohistochemistry, the tumour cells were overtly positive for CD3 (C), CD5 (D), and CD4 (E), and were weakly positive for bcl-6 (F) and PD-1 (G), while the CD23-immunopositive follicular dendritic cell meshwork (H) was irregularly expanding (immunohistochemical stainings, ×100; insets, ×400).

expanding (Figure 2H). The Epstein–Barr virus-encoded small RNAs in situ hybridisation stain was completely negative for lymphoma cells. Based on the above features, we finally made a conclusive diagnosis of systemic AITL accompanied by lymphomatous pleural effusions. One and half months later, the patient died with exacerbating dyspnoea, before treatment was started with chemotherapy.

3 | DISCUSSION

It is well known that AITL could be complicated with not only serous effusions but rarely with lymphomatous effusion.[1,2] However, there are only a few case reports in which detailed cytological examination has been described.[3,4] We did not find any case reports or studies in which effusion AITL cells were identified by the methodology of cell transfer technique and immunocytochemistry. When complicated effusion is first recognised, and the cytological diagnosis of a few atypical lymphoid cells is very difficult due to the insufficient/inadequate volume, lymphomatous effusion caused by AITL could be considered as one of the differential diagnoses. Besides, immunocytochemical staining to detect CD3/5/4 should be performed with the use of a cell transfer method. In fact, re-examination of our case allowed us to focus on a very small number of atypical medium-to-large, round to ovoid lymphocytes, which were not seemingly appreciated at the time of the initial diagnosis.

According to the first and largest series regarding lymphomatous effusion related to AITL, most recently published by Li et al,[2] two patterns of cytomorphology have been proposed, even though they also consider that the challenging cytological diagnosis of AITL effusion reveals a significantly broad spectrum, mimicking a variety of reactive and/or neoplastic processes. Li et al's "pattern 1" shows small to medium-sized ovoid to irregular lymphocytes varying in the number of apoptotic cells or mitoses, without any evidence of Hodgkin/Reed-Sternberg cells. On the other hand, "pattern 2" reveals the appearance of characteristic Hodgkin/Reed-Sternberg cells having multi-lobated nuclei, together with medium-sized ovoid

to irregular lymphocytes, and prominent apoptotic features and numerous mitotic figures. Based on these descriptions, the cytological findings of the present AITL case would be consistent with pattern 1, since we were not able to recognise any Hodgkin/Reed-Sternberg cells, and there were no remarkable apoptotic or mitotic activities. Furthermore, Yamagata et al have reported the cytological findings of lymphomatous effusion resulting from AITL, revealing the appearance of atypical plasma cells varying in size and shape, such as cells that were irregularly enlarged and/or with two nuclei.[5] The present case is most likely in agreement with the above features.

The expressions of follicular helper T-cell markers, including PD-1, CD10, bcl-6 or CXCL-13, are very useful for the definitive diagnosis of lymphomatous effusion caused by AITL, according to the first case report diagnosed by cell block immunohistochemistry.[3] In addition, when submitted effusion is sufficiently available for various examinations, clinicians/cytopathologists should perform not only immunohistochemistry but flow cytometry or next-generation sequencing studies.[7] In fact, flow cytometry can also play a key role for confirmation of the final diagnosis of AITL effusion, after ruling out the differential diagnoses (including B-cell lymphoma, Hodgkin lymphoma, natural killer lymphoma, other T-cell lymphomas, poorly differentiated carcinoma, or malignant melanoma). Nevertheless, because of the insufficient/inadequate amount of submitted pleural effusion in the current case, only 10 mL, we were never able to make cell block sections or perform additional immunocytochemistry. Therefore, we cytopathologists have to suggest taking a larger volume of specimen to clinicians, in order to obtain an accurate and correct diagnosis of malignant effusion of AITL. Actually, suspicion of AITL effusion requires a multidisciplinary approach, since we have more or less realised the limitations of cytomorphologically conclusive diagnosis.

AUTHOR CONTRIBUTIONS

Sohsuke Yamada and Kinue Takebayashi participated in the conception of the case study and writing of the manuscript. Sohsuke Yamada, Kinue Takebayashi, Rie Kadoguchi, Akihiro Shioya, and Takeru Oyama performed the clinical imaging and/or cytological/pathological/immunocytochemical interpretation of this tumour lesion. All of the authors have read and approved the final manuscript.

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CONFLICT OF INTEREST STATEMENT

No conflicts of interest are declared.

DATA AVAILABILITY STATEMENT

There is no sharing of data in connection with this manuscript.

INFORMED CONSENT

Written informed consent was obtained from the patient for their anonymised information to be published in this article.

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