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Angioimmunoblastic T-cell lymphoma induced hemophagocytic lymphohistiocytosis and disseminated intravascular coagulopathy: A case report

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Abstract

BACKGROUND

Angioimmunoblastic T-cell lymphoma (AITL) is a subtype of peripheral T-cell lymphoma, with heterogenous clinical manifestations and poor prognosis. Here, we reported a case of AITL-induced hemophagocytic lymphohistiocytosis (HLH) and disseminated intravascular coagulopathy (DIC).

CASE SUMMARY

An 83-year-old man presented with fever and purpura of both lower limbs for one month. Groin lymph node puncture and flow cytometry indicated a diagnosis of AITL. Bone marrow examination and other laboratory-related indexes indicated DIC and HLH. The patient rapidly succumbed to gastrointestinal bleeding and septic shock.

CONCLUSION

This was the first reported case of AITL-induced HLH and DIC. AITL is more aggressive in older adults. In addition to male gender, mediastinal lymphadenopathy, anaemia, and sustained high level of neutrophil-to-lymphocyte ratio may indicate a greater risk of death. Early diagnosis, early detection of severe complications, and prompt and effective treatment are vital.

Key Words: Angioimmunoblastic T-cell lymphoma; Hemophagocytic lymphohistiocytosis; Disseminated intravascular coagulopathy; Prognostic factors; Case report

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Core Tip: Angioimmunoblastic T-cell lymphoma (AITL) is a subtype of peripheral T-cell lymphoma, with heterogenous clinical manifestations and poor prognosis. Early diagnosis is particularly important. Herein, we reported a patient with AITL-induced hemophagocytic lymphohistiocytosis (HLH) and disseminated intravascular coagulopathy (DIC). The patient rapidly succumbed to gastrointestinal bleeding and septic shock. The time between onset and death was about a month. To the best of our knowledge, this was the first case of AITL-induced HLH and DIC. AITL is more aggressive in older adults. In addition to male gender, mediastinal lymphadenopathy, anaemia, and sustained high level of neutrophil-to-lymphocyte ratio may indicate a greater risk of death. Early diagnosis, early detection of severe complications, and prompt and effective treatment are vital.

INTRODUCTION

Angioimmunoblastic T-cell lymphoma (AITL) is a subtype of peripheral T-cell lymphoma (PTCL), which accounts for 1%-2% of non-Hodgkin's lymphoma and 15%-20% of PTCL[1], and presents with heterogenous clinical manifestations and poor prognosis[2]. Early diagnosis is particularly important. Herein, we reported a patient with AITL-induced hemophagocytic lymphohistiocytosis (HLH) and disseminated intravascular coagulopathy (DIC).

CASE PRESENTATION

Chief complaints

An 83-year-old man presented with fever and purpura of both lower limbs for one month (Figure 1A).

History of present illness

The patient presented with fever and purpura of both lower limbs for one month. He had chills and fever, with the highest body temperature of 40 °C, accompanied by cough and phlegm, no nausea and vomiting, no abdominal distention, abdominal pain, dizziness, headache and other discomfort.

History of past illness

The patient was diagnosed with diabetes mellitus for more than one month, had a history of hypertension for more than 30 years, coronary heart disease for 10 years, and renal insufficiency for many years. He denied any history of tuberculosis.

Physical examination

Physical examination showed mild anemia appearance, neck, armpit, groin lymph node enlargement, splenomegaly, edema and visible purpura of both lower limbs, without other special manifestations.

Laboratory examinations

Groin lymph node puncture showed disappearance of normal structure of lymph nodes and heterogeneous infiltration of small to medium-sized lymphoma cells, with proliferation of eosinophils (Figure 1B). The lymphoma cells were positive for CD3, CD4, CD10, and PD1, but negative for CD7 and CD8 by flow cytometry (Figure 1C). Bone marrow examination showed hemophagocytosis (Figure 1D) without evidence of lymphoma involvement.

The hemoglobin concentration and platelet count in the patient declined rapidly, with a minimum value of 65 g/L and 53 × 10^9/L, respectively. A serological examination showed hypertriglyceridemia (triglycerides 3.14 mmol/L), normal value of serum ferritin (299.50 μg/L), elevated levels of soluble interleukin (IL)-2 receptor (16080 U/mL), and hypergammaglobulinaemia. The capillary electrophoresis revealed monoclonal IgG Kappa (Figure 1E), without evidence of monoclonal plasma cells in bone marrow and lymph nodes. The coagulation function examination rapidly showed maximum level of D-Dimer (3.85 mg/L), prolonged prothrombin time (52.6 s), prolonged activated partial thromboplastin time (54.1 s), maximum value of International Normalized Ratio (4.57) and hypofibrinogenemia (Fibrinogen 1.2 g/L). The dynamic changes of white blood cell (WBC) count, lymphocyte cell count, neutrophil count, and neutrophil-to-lymphocyte ratio (NLR) from nearly onset to death are listed in Table 1.

Imaging examinations

Positron emission tomographies showed splenomegaly, generalized lymphadenopathy and enhanced activity in the posterior pharyngeal wall, bilateral neck, hilum of lung and mediastinum, pelvic wall, mesenteric lymph nodes and groin, suggestive of lymphoma (Figure 2).

FINAL DIAGNOSIS

Therefore, there was a clear indication of AITL-induced HLT and DIC.

TREATMENT

The patient's son signed the informed consent to refuse treatment.

OUTCOME AND FOLLOW-UP

The patient rapidly succumbed to gastrointestinal bleeding and septic shock. The time between onset and death was about a month.

DISCUSSION

AITL is aggressive, mainly affects older individuals (median age of 65 years), with a median survival of < 3 years[2,3]. The survival time of our patient was only about a month from onset to death. This was rare and indicated that the disease course was very aggressive.

A few studies reported that AITL was associated with plasma cell proliferation[4-6]. Monoclonal immunoglobulins were detected in this case, without evidence of monoclonal plasma cells. We speculated that AITL related to immunoregulatory disorder stimulated clonal plasma cell proliferation, but may be undetectable. However, the mechanism involved in the development of the concomitant monoclonal immunoglobulins remains to be clarified. High levels of cytokines, such as IL-6, IL-10, and TNF-α, may serve as possible contributing factors[4,5,7-10]. Whether the concomitant plasma cell proliferation indicated a poor prognosis in AITL deserves further investigation.

There were few reported cases of AITL-associated HLH. One study reported that HLT occurred in a 57-year-old man with AITL during chemotherapy. He subsequently developed multi-organ failure and died after a few days[11]. Another case report described an AITL patient who relapsed with HLH two months after receiving chemotherapy supported by autologous peripheral blood stem cell transplantation (PBSCT). The patient was successfully treated with allogeneic PBSCT with reduced intensity conditioning regimen[12]. Including our case, three cases of AITL-induced HLH were confirmed at the time of AITL diagnosis, not during chemotherapy

or relapse[13,14]. The clinical features of the three cases are listed in Table 2 (patients 1, 2, and 4. Patient 4 was the present case). HLH is a life-threatening severe complication of AITL. AITL lymphoma cells may produce cytokines and chemokines that cause systemic complications[15]. Epstein-Barr virus (EBV)-infected lymphocytes have been reported in up to 97% of AITL cases[16,17]. EBV infection may suggest a possible role for the virus in the etiology. EBV DNA was detectable in these three cases (Table 2). AITL-associated HLH had a poor prognosis due to aggressive disease course, especially in the presence of EBV infection, in conjunction with genetic abnormalities and immune dysfunction[16]. Patients 1 and 2 were successfully treated with etoposide together with CHOP regimen and allogeneic HSCT with RIC, respectively. However, our patient (patient 4) had AITL-associated HLH with concomitant DIC, and rapidly succumbed to gastrointestinal bleeding and septic shock. There was only one AITL-induced DIC case reported previously[18]. The clinical features of the case are listed in Table 2 (patient 3). DIC was mostly caused by sepsis, shock, solid cancer, and hematological malignancies[19,20]. When associated with hematological malignancy, DIC was most frequently accompanied by nearly 70% of newly diagnosed acute promyelocytic leukemia (APL)[21], followed by non-APL acute myeloid leukemia (17%) and non-Hodgkin's lymphoma (11%)[22,23]. Coagulopathy with hypofibrinogenemia could also occur with HLH. We could not exclude that DIC was part of the HLH process in our patient. The disease course was very aggressive accompanied by DIC. Patient 3 succumbed to DIC and fatal gastrointestinal bleeding. Both of patient 3 and patient 4 had very poor diagnosis.

The risk of death increased and treatment effectiveness decreased with age. Patient 4 was the oldest, followed by patient 3. To the best of our knowledge, our patient was the first case with AITL-induced HLH and DIC. Survival was

significantly related to age, male gender, mediastinal lymphadenopathy and anaemia[2,24] which were adverse prognostic factors in our patient. Notably, NLR in AITL was a significant, independent prognostic factor for overall survival (OS), when NLR ≥ 2.2 indicated shorter OS[25]. Table 1 shows that the level of WBC in our patient was almost within the normal range, whereas lymphocyte count was consistently at a low level and NLR was significantly high from nearly onset to death. We speculated that the patient suffered from severe immunosuppression, and the risk of death was greater when NLR was irreversibly sustained high. Consequently, HLH and DIC were induced, which resulted in rapid and fatal septic shock and gastrointestinal bleeding.

CONCLUSION

AITL is more aggressive in older adults. In addition to male gender, mediastinal lymphadenopathy, anaemia, and sustained high level of NLR may indicate a greater risk of death. Early diagnosis, early detection of severe complications, and prompt and effective treatment are vital.

Figure 1 Examinations. A: Purpura were observed on both lower limbs of the patient; B: Groin lymph node puncture specimen showed the normal structure of lymph nodes disappeared and heterogeneous infiltration of small to medium-sized lymphoma cells, with proliferation of eosinophils (hematoxylin and eosin stain, × 40); C: Flow cytometry: Neoplastic T cells were shown in red and benign T cells in blue (analysis was gating on lymphocytes). The neoplastic T cells were positive for CD3, CD4, CD10, and PD1, but negative for CD7 and CD8; D: Bone marrow examination showed hemophagocytosis; E: The capillary electrophoresis revealed monoclonal IgG Kappa.

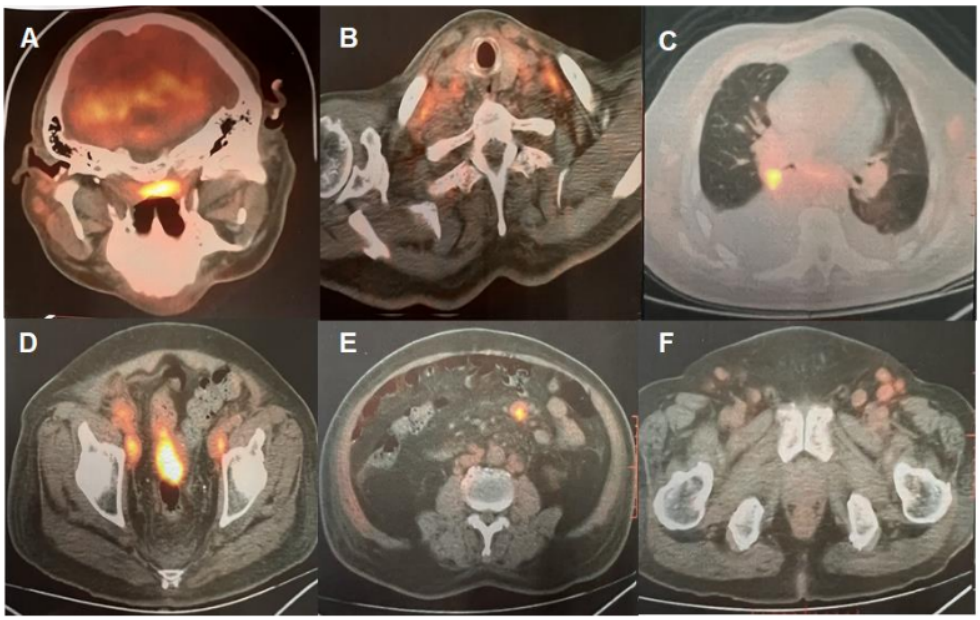

Figure 2 Positron emission tomographies. A-F: Positron emission tomographies showed generalized lymphadenopathy, enhanced activity in posterior pharyngeal wall (A), bilateral neck (B), hilum of lung and mediastinum (C), pelvic wall(D), mesenteric lymph nodes (E), and groin (F).

Table 1 Dynamic change of white blood cell, lymphocyte cell count, neutrophil count, neutrophil-to-lymphocyte ratio of the present patient

Index date	WBC (× 10^9/L)	Lymphocyte cell count (× 10^9/L)	Neutrophil count (× 10^9/L)	NLR
4-9	7.59	0.10	7.26	72.6
4-14	4.78	0.48	3.98	8.29
4-22	5.22	0.21	4.85	23.01
4-25	5.14	0.34	3.90	11.47
4-27	3.83	0.33	2.89	8.76
4-29	5.77	0.32	4.74	14.81
5-1	5.19	0.40	4.61	11.53

WBC: White blood cell; NLR: Neutrophil-to-lymphocyte ratio.

Table 2 Clinical features of angioimmunoblastic T-cell lymphoma patients with hemophagocytic lymphohistiocytosis or disseminated intravascular coagulopathy

	Patient 1	Patient 2	Patient 3	Patient 4 (the present case)
Sex/age (yr) at the time of diagnosis	53/male	62/female	72/female	83/male
Laboratory findings in peripheral blood				
% atypical lymphocytes in the blood of all lymphocytes	9%	NA	NA	NA
Hypereosinophilia (%)	NA	NA	Yes (17%)	Yes (9%)
Autoantibody	Antinuclear; antibodies; antiNAdoubleNAstranded; DNA antibodies were negative	NA	NA	Anti TIF-1γ; antibodies; anti Jo-1 antibodies were positive
Hypergammaglobulinaemia	Yes (polyclonal)	NA	Yes (polyclonal)	Yes (monoclonal)

EBV DNA copies (IU/mL)	8.42×10^4	NA, but positive in lymph node biopsy	NA	131
Immunophenotype/immunohistochemical staining	CD2+, CD3+, CD5+, CD7+, CD10+; CD20dim, pairedNAboxvdomain 5 dim and telomerase B dim (biopsies of the left cervical lymph node)	CD3+, CD4+, CD8NA, CD30NA, CD56NA, CD20NA (cervical lymph node biopsy)	CD4+, CD5+, CD10+ (lymph node)	CD3+, CD4+, CD10+, PD1+, CD7NA, CD8NA (lymph node)
Clinical manifestation				
Generalized lymphadenopathy	Yes	Yes	Yes	Yes
Bone marrow involvement	Hemophagocytosis and abnormal lymphocytes	Hemophagocytosis, but without evidence of lymphoma	No lymphoma infiltration and no evidence of hemophagocyt	Hemophagocytosis, but without; evidence of lymphoma involvement

		involvement	osis, two weeks late, bone marrow infiltration	
Hepatomegaly	Yes	Yes	Yes	No
Splenomegaly	Yes	Yes	Yes	Yes
Skin rash /purpura	Yes	NA	NA	Yes
Pleural effusion	NA	NA	NA	Yes
Severe complication				
HLH	Yes	Yes	No	Yes
DIC	No	No	Yes	Yes
Therapy	Etoposide together with CHOP regimen	CHOP, mesna, ifosfamide, mitoxantrone, etoposide; allogeneic HSCT with RIC	Steroids	AntiNAinfection and other symptomatic treatment
Outcome	Successfully treated	Successfully treated	Succumbed to DIC, fatal	Succumbed to gastrointestinal bleeding, septic shock

							gastrointestinal bleeding.

NA: Not available; CHOP: Cyclophosphamide, doxorubicin, vincristine, and prednisolone; EBV: Epstein-Barr virus; HLH: Hemophagocytic lymphohistiocytosis; ; DIC: Disseminated intravascular coagulopathy; HSCT: Hematopoietic stem cell transplant; RIC: Reduced-intensity conditioning.

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