



Fever, rash, and eosinophilia – early signs of angioimmunoblastic T-cell lymphoma

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Abstract

Angioimmunoblastic T-cell lymphoma (AITL) is an uncommon lymphoma of elderly adults with a poor prognosis. AITL patients show systemic symptoms, lymphadenopathy, and not infrequently, skin rash with various dysimmune phenomena rashes. The case is presented of a 68-year-old male with skin rash, lymphadenopathy and hypereosinophilia who, after investigations, was diagnosed with AITL. Despite the treatment used, the patient's condition gradually deteriorated and died due to heart and kidney failure. The diagnosis of AITL is often established only after several weeks or months because of transient physical findings, non-specific symptoms, and a broad range of serologic or radiologic abnormalities. Some patients with AITL experience non-specific dermatitis and eosinophilia. The presented case should raise awareness of the presentations of AITL which is important for physicians to reach an accurate diagnosis.

Key words

lymphoma, eosinophilia, rash, fever, immunoblastic lymphadenopathy, hypereosinophilic syndrome, non-Hodgkin, exanthema

INTRODUCTION

Angioimmunoblastic T-cell lymphoma (AITL) is a peripheral T-cell lymphoma (PTCL) which, according to the 2016 revised WHO classification, belongs to nodal PTCL with a Follicular Helper (TFH) phenotype [1]. AITL accounts for only 1–2% of all cases of non-Hodgkin lymphomas [2]. After excluding primary cutaneous lymphomas and lymphomas with leukemic blood involvement, the overall incidence of AITL reaches 18.5% [3]. AITL is an aggressive neoplasm with a low 5-year survival of approximately 30–33% in most reported patient series [3, 4, 5]. AITL is a disease of elderly adults in their sixth or seventh decade of life with median age ranging from 65–69 years [3, 5]. At presentation, most patients (80–90%) have advanced-stage III – IV disease by the Ann Arbor classification [3, 5]. Some patients with AITL experience non-specific dermatitis and eosinophilia and might be referred to an allergist/internist. The case is presented to raise awareness of the presentations of AITL which is important for physicians to reach an accurate diagnosis.

CASE REPORT

The case is presented of a 68-year-old male with exacerbated chronic obstructive pulmonary disease (COPD), heart failure,

and type 2 diabetes mellitus, skin rash, lymphadenopathy and hypereosinophilia. According to the patient, the symptoms started three weeks before admission to our department. He recorded a rash, low-grade fever, abdominal pain, and diarrhea. Initially, the patient was hospitalized in a district hospital with a suspicion of bacterial sepsis, where he received systemic antibiotics. He was subsequently admitted to the Department of Internal Diseases. The medical history revealed hypertrophic cardiomyopathy, cardiac pacemaker implantation, percutaneous coronary intervention (PCI) on the left anterior descending (LAD) artery coronary because of coronary heart disease, and an episode of cerebral stroke. On admission, the patient presented a widespread rash consisting of erythematous and dusky papules, infiltrated plaques over the trunk, and proximities (Fig. 1a). There was also an admixture of purpuric lesions over the lateral aspects of the torso (Fig. 1b). Other abnormalities were enlargement of supraclavicular lymph nodes, lower limb oedema, rattles at the lungs' base, and abdominal distension. During hospitalization, the patient complained about abdominal pain and diarrhea.

Peripheral blood testing demonstrated leucocytosis up to 23.60 K/uL (reference range 4.0–10.0) with hypereosinophilia 3.960 K/uL (reference range 0.0–0.5 K/uL), anaemia (haemoglobin 11.1 g/dl, RBC 3.98 M/uL, MCV 82.5 fl (80.0–94.0 fl)) and reticulocytosis – 3.13% (0.50–2.00%). The levels of beta2 macroglobulin and lactate dehydrogenase (LDH) were elevated: 10.52 mg/l (reference range 0.7–3.0) and 635 IU/l (10–480 IU/l), respectively, as well as inflammatory markers: sedimentation rate (SR) – up to 85 mm/h (reference range 2–35 mm/h) and C-reactive

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Figure 1. Widespread rash consisting of erythematous and dusky papules infiltrated plaques over the trunk and proximities (Fig. 1a). There was also an admixture of purpuric lesions over the lateral aspects of the torso (Fig. 1b)

protein (CRP) – 86 mg/l (< 5 mg/l). Serum electrophoresis with immunofixation showed: alpha 1 globulin 7.7% (2.9–4.9%), alpha 2 globulin 12.4% (7.1–11.8%), gamma globulin 17.7% (11.1–18.8%), beta 1 globulin 6.1% (4.7–7.2), beta 2 globulin 21.8 % (3.2–6.5%). On immunofixation, there was weak monoclonal IgG lambda protein. Total IgE level concentration was 8569 IU/ml (0–100 IU/ml). The levels of individual immunoglobulins are presented in Table 1. The creatinine level was 2.6 mg/dl.

Multiple blood and urine cultures were negative. *C. Difficile* was not detected in the qualitative faecal test. The level of procalcitonin was 0.56 ng/ml.

The patient underwent chest and abdominal computed tomography (CT), which demonstrated numerous enlarged mediastinal lymph nodes (the largest one up to 25 × 32 mm, axillary (18 × 26 mm), and cervical lymph nodes (up to 11 mm), periaortic, iliac, and inguinal lymph nodes. There were also bands of parenchymal densities in the right and left lungs.

Cervical lymph node and skin biopsy were performed for histopathological testing. The lymph node histopathology showed angioimmunoblastic T-cell lymphoma (AITL), pattern 3 (Fig. 2 a-d). The immunohistochemical stainings of skin samples were also suggestive of cutaneous T-cell lymphoma (Fig. 3 a-d).

The myelogram showed an increase in the percentage of eosinophilic granulocytes and decreased percentage of red blood cells.

Table 1. Levels of individual immunoglobulins in the presented patient

Immunoglobulin	Result	Reference range	Units
IgE		(0–100)	IU/ml
IgA	9.06	(0.845–4.99)	g/l
IgG	11.4	(6.10–16.16)	g/l
IgM	3.35	(0.35–2.42)	g/l

Electrocardiography disclosed atrial fibrillation, while echocardiography disclosed left ventricular hypertrophy. The global systolic function of the left ventricle was normal. The level of NT-proBNP increased from 5155 pg/ml on admission to 15162 pg/ml (0–352 pg/ml) due to progressing heart failure.

Despite the treatment used, the patient's condition gradually deteriorated and he died due to heart and kidney failure.

DISCUSSION

AITL in most patients presents as a subacute or acute systemic illness often associated with generalized lymphadenopathy, skin rash, and/or hepatosplenomegaly [6]. Generalized lymphadenopathy and B symptoms are present in 76–99 and 55–77% of patients, respectively [2]. Lymph node enlargement visualized by computer tomography is often modest (1–3 cm) [2, 7]. 60% of patients have bone marrow

involvement [8]. Hepatosplenomegaly is found in one-third of affected individuals, and two or more extranodal sites are involved in at least one-fifth of cases [9]. In the presented case, CT results were in line with those reported in the literature – the largest mediastinal lymph nodes reached up to 30 mm in diameter. There was no hepatosplenomegaly or bone marrow involvement; the skin was the only biopsy-proven extranodal site of involvement.

Regarding laboratory results at diagnosis, between 33–65% of patients are anaemic [8]. Other common findings include polyclonal, hypergammaglobulinemia, especially of the IgG type – (30–65%) [8], elevated inflammatory markers 67% [6], elevated LDH (60–71%) [3, 6], elevated B2-microglobulin (22–82%) [3, 6] and hypereosinophilia (32–34%) [2]. The presented patient had anaemia, elevated inflammatory markers, increased levels of LDH, B2-microglobulin, and hypereosinophilia. He had normal gamma globulins with concurrent monoclonal dysproteinemia, which is found in only 10% of patients [2].

Another peculiar laboratory finding was a high level of total serum immunoglobulin E (tsIgE). Scarce data suggest that total IgE levels could be elevated in almost half of AITL patients [10, 11]. Recent genetic findings demonstrated a T Follicular Helper (TFH) signature of AITL [12]. TH cells localized in B-cell follicles in the secondary lymphoid organs regulate antibody isotype switching, affinity maturation, and B-cell memory generation. Nowadays, IL-4+ TFH cells are believed to be indispensable for IgE production [13]. Thus, aberrant TFH activity could be responsible for the dysimmune phenomena encountered in AITL, including IgE hypergammaglobulinemia [14].

Unfortunately, AITL symptoms may suggest autoimmune, infectious, or allergic diseases, which leads to delay of diagnosis (median time 3.6 months) [6]. Many of the patients reported in the literature also have an antecedent history of antibiotic intake [6]. The presented case exemplifies the possible diagnostic challenges posed by AITL patients. The disease onset was heralded by relatively non-specific findings – a widespread cutaneous rash, low-grade fever, moderate peripheral lymphadenopathy, and abdominal complaints with diarrhea.

On admission to the Department for Internal Diseases, the skin lesions were the most prominent sign. Cutaneous manifestations are the most common extranodal expressions in AITL patients occurring in up to 50% of cases [15] and not infrequently are the presenting complaint (up to 70% of patients) [16]. The skin involvement by AITL is polymorphic and often non-specific, commonly consisting of maculopapular eruption that may mimic drug reaction or viral exanthema [6, 16, 17]. In general, there are three main categories of skin findings in AITL macular, papular, plaque-like- nodular lesions [15], or mixed features of those above [18]. In a recent retrospective analysis, 48.8% of AITL patients had skin involvement, most frequently in the form of a non-specific rash (57.1%), followed by papular (23.8%), erythrodermic (16.7%), nodular (9.5%) and petechial/ purpuric (7.1%) efflorescences [17]. The presented patient had a combination of papules, indurated plaques, and haemorrhagic lesions (Fig. 1 a-b). Reports on the effect of skin involvement in the survival of patients with AITL vary. Some noted that skin rash was associated with shorter survival [19, 20].

Diagnosis of AITL is typically based on lymph node biopsy. In the presented patient, the picture of lymph node biopsy

was consistent with a diagnosis of AITL (Fig. 1 a-d) (pattern III, AITL without follicles). Characteristic nodal features of AITL like capillary hyperplasia and atypical lymphocytes with clear cytoplasm are rare in cutaneous biopsies. Two skin biopsies taken from infiltrated papule and purpuric skin lesion showed dense perivascular and sparse periadnexal dermal infiltration of medium-sized lymphocytes, which corresponded with the involvement of the skin by the AITL (Fig. 3 a-d). Histopathologically, cutaneous AITL (cAITL) shows dermal, perivascular infiltrates of small and medium-sized lymphocytes with no or minimal epidermotropism. Less frequently, the neoplastic cells are also located periadnexally [18].

The differential diagnosis of a patient with a skin rash, eosinophilia, and systemic symptoms is broad. Drug reaction with eosinophilia and systemic symptoms (DRESS) and lymphocytic variant-HES are two differential considerations in such cases. DRESS is a rare, potentially life-threatening, adverse drug reaction characterized by skin rash, fever, lymphadenopathy, haematological abnormalities, and internal organ involvement [21, 22]. Strikingly, some AITL patients may even meet the DRESS criteria. However, in contrast to DRESS, angioimmunoblastic T-cell lymphoma patients show low drug causality probability, lesser hepatic involvement, more large-sized lymphadenopathy, and more frequent splenomegaly [23]. In the presented case, neither medication history nor liver injury was consistent with DRESS syndrome. Next, the patient's skin involvement pattern did not correspond to the typical morbilliform rash in DRESS syndrome. Finally, mediastinal lymphadenopathy, which raised concern for lymphoma in the presented case, has been rarely reported in DRESS [24].

Hypereosinophilic syndrome (HES) is a multisystem disease with a broad spectrum of cutaneous, pulmonary, and less frequently, gastrointestinal, cardiac, and neurologic manifestations [25]. HES is a diagnosis of exclusion after neoplastic, infectious, autoimmune, and drug-related hypersensitivity etiologies have been ruled out [25]. It can involve nearly every organ system and develop insidiously over time, or present acutely and progress rapidly [26]. Lymphocytic-variant of HES (LV-HES) is a subtype of HES defined by the detection of the immunophenotypically aberrant, usually monoclonal T-cell population [27]. Most patients have elevated IgE [28]. Skin histology is often uncharacteristic, and morphologic changes in the lymph nodes could mimic AITL [29]. Thus, the differential diagnosis with AITL is not always easy. The discussed patient had histopathologically confirmed lymphoma, excluding HES. In contrast to LV-HES, AITL is a disease of older individuals with a more aggressive course. Cutaneous manifestations of LV-HES include pruritus, angioedema, urticaria, eczematous dermatitis, and papular lesions. Patients with LV-HES rarely suffer from palpable purpura and the indurated plaques described in the presented case [30]. In doubtful cases, staining with TFH markers on lymph node biopsy should aid the correct diagnosis [29]. Unfortunately, at that time, such immunofluorescence markers for TFH cells were unavailable in the hospital where the patient was treated.

A variety of conditions may be accompanied by eosinophilia. Overall, allergy/atopy or drug hypersensitivity and helminth infections are the first and second most prevalent reasons for eosinophilia, respectively [31, 32, 33], but usually result in mildly elevated AEC (less than

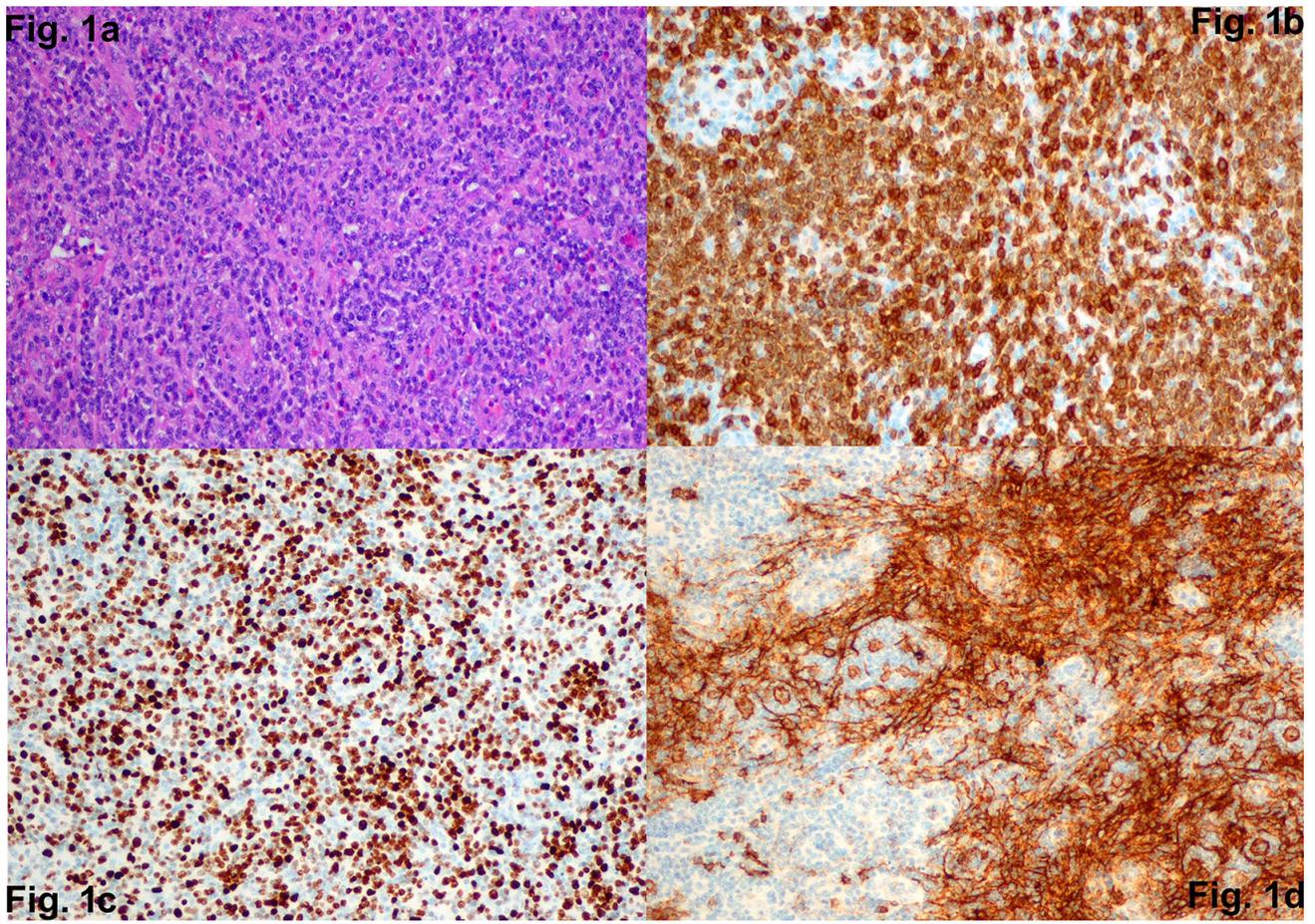


Figure 2. (a) Lymph node involvement in angioimmunoblastic T-cell lymphoma; (b) Immunoexpression of CD3 in lymphoma cells with (c) high proliferative index (Ki67); (d) Immunoexpression of CD23 proliferation of follicular dendritic cells meshwork (objective magnification a, b, c, d – $\times 20$)

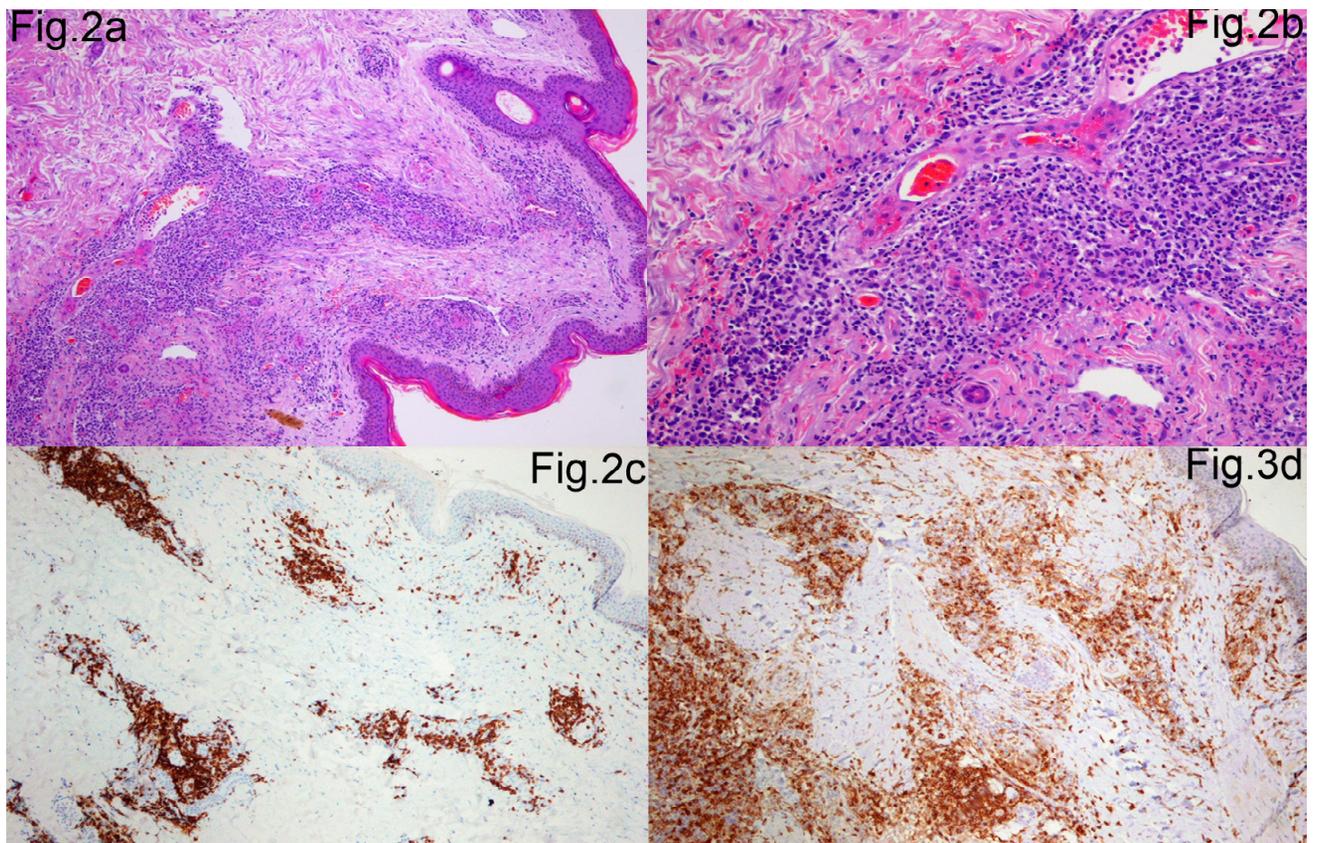


Figure 3. (a-b) Skin involvement in angioimmunoblastic T-cell lymphoma. Immunoexpression of (c) CD3 and (d) CD4 in lymphoma cells (objective magnification a, c, d – $\times 5$, b – $\times 20$)

1.5 × 10⁹/l [34]. However, the higher the eosinophile count, the higher the incidence of hypereosinophilia-associated disease. Hypereosinophilia (HE) is defined by a marked increase in eosinophils in PB, ≥1.5 × 10⁹/L [35]. The presented patient had substantially elevated numbers of eosinophils, fulfilling the criterion for hypereosinophilia. Eosinophilia can accompany haematological malignancies either as a primary clonal condition or as a secondary, reactive process [36]. Non-myeloid malignancies may be associated with secondary eosinophilia driven by the abnormal production of cytokines and growth factors, usually by the tumour cells [29, 37]. Published case series revealed that the severity of initial eosinophilia makes a significant difference in the odds ratio of being diagnosed with a haematologic malignancy [36, 38]. In a study by Jin et al. [36], the overall frequency of haematologic malignancy among adults with eosinophilia was 0.2%, but raised substantially to 5.1% in hypereosinophilia. In the same study, AITL was the most prevalent entity among non-Hodkin's lymphomas (NHLs) encountered in patients presenting with eosinophil counts above 1,5 × 10⁹/L [36]. Overall, an increased number of eosinophils is seen in one-third of the AITL cases at the time of diagnosis [2].

CONCLUSIONS

HE encompasses a broad range of differential diagnoses and may require consultations from various specialists (e.g. haematology, dermatology, pulmonology, gastroenterology, and neurology). Initial workup should determine the onset, duration, and magnitude of the eosinophilia, together with associated symptoms [39]. A detailed history of recent exposures to infections and medications is mandatory. Systemic symptoms, such as fever, night sweats, and weight loss, may suggest malignancy [39]. In any doubtful case of skin rash and lymphadenopathy, early lymph node biopsy is advisable to exclude the possibility of AITL.

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