Skin lesions and neutrophilic leukemoid reaction in a patient with angioimmunoblastic T-cell lymphoma: a case report and review of the literature

Jianming He & Houjie Liang
Department of Oncology and Southwest Cancer Center, Southwest Hospital, Third Military Medical University, Chongqing, China

Correspondence
Houjie Liang, Department of Oncology and Southwest Cancer Center, Southwest Hospital, Third Military Medical University, Chongqing 400038, China. Tel/Fax: +86 23 68754128; E-mail: lianghoujie@sina.com

Funding Information
No sources of funding were declared for this study.

Received: 17 December 2014; Revised: 26 February 2015; Accepted: 03 March 2015

Clinical Case Reports 2015; 3(6): 483–488

doi: 10.1002/ccr3.273

Introduction
Angioimmunoblastic T-cell lymphoma (AITL) is categorized as a peripheral T-cell lymphoma and is clinically characterized by a sudden onset of constitutional symptoms, lymphadenopathy, hepatosplenomegaly, immune disease (hyperactivity of the immune system and immunodeficiency) and pleural effusion, ascites, and edema [1–3]. Up to approximately half of patients have skin lesions but vesicles directly caused by AITL are rare [1, 3–5]. Elevated white blood cells (usually eosinophilia) are also often observed in laboratory investigations but to our knowledge, neutrophilic leukemoid reaction caused by AITL was not reported, yet [1–3, 6, 7].

Here, we present an AITL case presenting with rare skin lesions (including vesicles, papulovesicles, and miliary papules) symmetrically distributed on the extremities and trunk, with more distal lesions increasing in severity and neutrophilic leukemoid reaction.

Case Report
A 53-year-old Asian man was referred to our hospital for evaluation of lymphadenopathy and skin lesions. The patient’s symptom history was detailed as follows: a dry cough for 3 months, lymphadenopathy for 1 month, skin lesions (started from the extremities) accompanied by pruritus for 3 weeks, dyspnea, and a mild fever for 1 week. At the time of admittance to our hospital, the patient endured severe pain of vesicles on hands and feet. Upon examination, the skin lesions were symmetrically distributed, with more distal lesions increasing in severity. Some large vesicles containing dark reddish exudate were distributed on both fingers and feet (Fig. 1A and B). Some vesicles (large and small) and papulovesicles containing clear transparent exudate were distributed on the extremities (Fig. 1A and C). Miliary papules were distributed on the upper chest and lower abdomen. Few lesions were found in the face while skin lesions were not found in the palms, soles, genitalia, scalp, around the mouth, or oral mucosa. There were palpable superficial lymph nodes in the neck, axillary fossae, and inguinas. The temperature of the skin was between 37.0 and 38.5°C during his hospitalization. The routine blood test showed a white blood cell count of 44.43 × 10⁹/L, red blood cell count of 5.02 × 10¹²/L, and platelet count of 214 × 10⁹/L. The cytological study of bone marrow showed hypergranulopoiesis. A computed tomography scan of the chest
revealed lymphadenopathy in the mediastinum and axillary fossae (Fig. 2A–C). Immunochemistry of biopsy from cervical lymphadenopathy showed CD3 was diffuse strong positive, CD20 and CD8 was scattered positive, CD21 and Bcl-2 were focally positive, and Ki67 positive cells ratio was higher than 80%. Based on the cytological study of bone marrow, peripheral blood, immunochemistry and hematoxylin & eosin staining of lymphadenopathy (Fig. 2D), the pathologic diagnosis was AITL.

Both morphine and tramadol were used to control pain. After 4 days of intravenous latamoxef sodium and isepamicin treatment, the routine blood test showed a white blood cell count of 58.97 × 10^9/L (neutrophils% 91.64%, lymphocytes% 5.24%, monocytes% 2.44%, and eosinophils% 0.42%), red blood cell count of 4.50 × 10^12/L, and platelet count of 177 × 10^9/L. Manifestations progressively aggravated. Then chemotherapy consisting of cyclophosphamide, epirubicin, vincristine, and prednisone (CHOP-like therapy) was administered. After chemotherapy, there was abatement of clinical manifestations. The number of skin lesions increased during his 9 days of hospitalization. Some vesicles were blisters in the beginning, without erythematous or hemorrhagic base. Some papules on extremities slowly became papulovesicles and it usually took 1 week. None of papules on the trunk became papulovesicles or vesicles. The patient abandoned further treatment.

**Discussion**

AITL is a rare malignancy accounting for about 2% of all non-Hodgkin lymphoma and a highly aggressive neoplasm of the elderly [1–3, 8]. The median patients’ age is approximate 65 years [1–3, 8, 9]. It generally presents with lymphadenopathy and is almost always accompanied by concomitant symptoms, including B symptoms, skin lesions, splenomegaly, hepatomegaly, effusion/edema/ascites, anemia, thrombocytopenia, elevated LDH, hypergammaglobulinemia and so on (Table 1).

Nearly half of AITL patients have skin lesions [1, 3–5, 8]. Skin lesions can precede, follow or be concurrent to lymphadenopathy [5, 10, 11]. AITL skin lesions do not have characteristics to enable it to be distinguished from other skin eruptions, especially from drug eruptions. Therefore, misdiagnosis is not rare [5, 12–14]. Since AITL is almost always accompanied by concomitant symptoms (Table 1), to be
familiar with the common clinical characteristics and types of skin lesions is greatly helpful to avoid misdiagnosis. Skin lesions in AITL usually accompany pruritus [1–5, 8]. Typical lesions are usually a generalized morbilliform or maculopapular eruptions on the trunk mimicking toxic erythema [2, 4, 5, 8]. In the literature, uncommon skin lesions of AITL are mostly described in case reports or review articles (Table 2). It is not rare that the patient has a generalized pleomorphic rash composed of several types of rashes, such as macula, papules, maculopapules,

Table 1. Clinical manifestations of AITL (numbers are presented as % except Patient number and Age).

| Authors                  | Federico [1] | Tokunaga [2] | Mourad [3] | Lachenal [9] | Siegert [4] | Aozasa [25] |
|--------------------------|--------------|--------------|------------|--------------|-------------|-------------|
| Patient number           | 243          | 207          | 157        | 77           | 62          | 44          |
| Age, years               | Mean         | 65           | 67         | 62           | 64.5        | 64          |
|                          | Range        | 20–86        | 34–91      | 20–89        | 20–91       | 21–87       |
| Male sex                 | 56           | 64           |            | 56           | 58          | 55          |
| Lymphadenopathy          |              |              |            |              |             |             |
| Generalized              | 76           |              | 90         |              |             |             |
| Localized                | 24           |              | 9          |              |             |             |
| Skin rash                | 21           |              | 44         | 45           | 49          | 27          |
| B symptoms               | 69           | 60           | 72         | 77           | 68          |             |
| Splenomegaly             | 35           |              | 51         |              | 39          |             |
| Hepatomegaly             | 26           |              | 26         |              | 52          |             |
| Effusion/edema/ascites   | 14           | 26           | 25         | >38          |             |             |
| Bone marrow involvement  | 28           | 29           | 47         |              |             |             |
| Extranodal sites, >1     | 27           | 23           | 46         |              |             |             |
| Anemia                   | 33           | 61           | 65         | 51           | 57          | 20          |
| Platelet count < 150 x 10^9/L | 25   | 34           | 20         |              | 20          |             |
| Elevated LDH             | 60           | 75           | 66         | 71           | 70          |             |
| Elevated C-reactive protein | 35        | 46           | 67         |              |             |             |
| Hypergammaglobulinemia   | 30           | 50           | 51         | 51           | 64          |             |
| Positive Coombs test     | 13           | 46           | 33         | 33           | 58          | 32          |

LDH, Lactate dehydrogenase.

Table 2. Uncommon skin lesions of AITL.

| Authors                  | Age/Gender | Skin lesions                                         | Duration of skin lesions before/after onset of lymphadenopathy | Prognosis          |
|--------------------------|------------|------------------------------------------------------|---------------------------------------------------------------|-------------------|
| Wechsler [29]            | 53/F       | Erythematous macules; petechiae; purpura             | 1 month after                                                | Died (23 month)   |
| Matloff [30]             | 77/M       | Macules; petechiae; purpura                          | 1 year before                                                | Alive (4 month)   |
| Seehafer [10]            | 74/M       | Petechiae                                            | Concurrent                                                   | Died (3 month)    |
| Seehafer [10]            | 61/M       | Erythroderma and purpura                             | Concurrent                                                   | Alive (48 month)  |
| Seehafer [10]            | 57/M       | Petechiae                                            | 10 month before                                              | Alive (48 month)  |
| Schmuth [31]             | 73/F       | Macules; petechiae; purpura                          | 4 week before                                                | Alive (4 month)   |
| Martel [15]              |            | Necrotic purpura, maculopapules and urticaria         |                                                               | Died (26 day)     |
| Martel [15]              |            | Pruritic papulovesicular (prurigo-like) lesion         |                                                               | Alive (96 month)  |
| Hashefi [32]             |            | Maculopapules, petechiae                             | 3 month before                                               | Died (23 month)   |
| Suarez-Vilela [33]       | 67/F       | Sarcoïdosis                                           | 1 month before                                               | Died (3 year)     |
| Huang [34]               | 62/M       | Erythroderma; plaques; nodules                        | 3 year after                                                 | Died (3 year)     |
| Jones [35]               | 67/M       | Erythroderma, toxic epidermal necrolysis              | Concurrent                                                   | Died (5 month)    |
| Tschatzis [36]           | 50/M       | Polyarthritis, subcutaneous nodules                   | Concurrent                                                   | Died (2 month)    |
| Jayaraman [11]           | 61/M       | Macules, papules, plaques, and nodules                | Concurrent                                                   | Alive (5 year)    |
| Ortonne [37]             | 63/F       | Nodules, gingival ulceration                          |                                                               |                   |
| Ortonne [37]             | 54/M       | Maculopapules, hemorrhagic/necrotic nodules           |                                                               |                   |
| Nassar [5]               | M/47       | Erythematous eruption; violaceous plaques with bullae containing pale yellow exude | 3 month before                                               | Alive (4 month)   |
| Smithberger [38]         | 79/F       | Cutaneous tumors and ulcerated nodules                | No lymphadenopathy                                           |                   |
| Ponciano [39]            | 36/M       | Erythematous plaques, sometimes annular               | 5 year before                                                | Alive (2 year)    |

© 2015 The Authors. Clinical Case Reports published by John Wiley & Sons Ltd.
The authors have no competing interest.

Conflict of Interest
References

1. Federico, M., T. Rudiger, M. Bellei, B. N. Nathwani, S. Luminari, B. Coiffer, et al. 2013. Clinicopathologic characteristics of angioimmunoblastic T-cell lymphoma: analysis of the international peripheral T-cell lymphoma project. J. Clin. Oncol. 31:240–246.

2. Tokunaga, T., K. Shimada, K. Yamamoto, D. Chihara, T. Ichihashi, R. Oshima, et al. 2012. Retrospective analysis of prognostic factors for angioimmunoblastic T-cell lymphoma: a multicenter cooperative study in Japan. Blood 119:2837–2843.

3. Mourad, N., N. Mounier, J. Briere, E. Raffoux, A. Delmer, A. Feller, et al. 2008. Clinical, biological, and pathologic features in 157 patients with angioimmunoblastic T-cell lymphoma treated within the Groupe d’Etude des Lymphomes de l’Adulte (GELA) trials. Blood 111:4463–4470.

4. Siegert, W., C. Nerl, A. Agthe, M. Engelhard, G. Brittinger, M. Tiemann, et al. 1995. Angioimmunoblastic lymphadenopathy (AILD)-type T-cell lymphoma: prognostic impact of clinical observations and laboratory findings at presentation. The Kiel Lymphoma Study Group. Ann. Oncol. 6:659–664.

5. Nassar, D., M. Gabillot-Carre, N. Ortonne, K. Belhadj, L. Ahsanuddin, A. N., R. K. Brynes, and S. Li. 2011. Peripheral blood polyclonal plasma hypergammaglobulinemia in patients with angioimmunoblastic T-cell lymphoma: report of 3 cases and review of the literature. Int. J. Clin. Exp. Pathol. 4:416–420.

6. Gardais, J., S. Fanello, F. Joubaud, and C. Simard. 1984. Leukemoid eosinophilic reaction in angioimmunoblastic adenopathy. Rev. Med. Interne 5:309–314.

7. Iannitto, E., A. J. Ferreri, V. Minardi, C. Tripodo, and H. H. Kreipe. 2008. Angioimmunoblastic T-cell lymphoma. Crit. Rev. Oncol. Hematol. 68:264–271.

8. Lachenal, F., F. Berger, H. Ghesquieres, P. Biron, A. Hot, E. Callet-Bauchi, et al. 2007. Angioimmunoblastic T-cell lymphoma: clinical and laboratory features at diagnosis in 77 patients. Medicine (Baltimore) 86:282–292.

9. Seeber, J., N. C. Goldberg, C. H. Dicken, and W. P. Su. 1980. Cutaneous manifestations of angioimmunoblastic lymphadenopathy. Arch. Dermatol. 116:41–45.

10. Jayaraman, A. G., D. Cassarino, R. Advani, Y. H. Kim, E. Tsai, and S. Kohler. 2006. Cutaneous involvement by angioimmunoblastic T-cell lymphoma: a unique histologic presentation, mimicking an infectious etiology. J. Cutan. Pathol. 33(Suppl. 2):6–11.

11. Imafuku, S., D. Yoshimura, Y. Moroi, K. Urabe, and M. Furue. 2007. Systemic varicella zoster virus reinfection in a case of angioimmunoblastic T-cell lymphoma. J. Dermatol. 34:387–389.

12. Kanzaki, Y., M. Eura, K. Chikamatsu, M. Yoshida, K. Masuyama, H. Nishimura, et al. 1997. Angioimmunoblastic lymphadenopathy-like T-cell lymphoma. A case report and immunologic study. Auris Nasus Larynx 24:199–206.

13. Kaneko, Y., R. A. Larson, D. Varaikojis, J. M. Haren, and J. D. Rowley. 1982. Nonrandom chromosome abnormalities in angioimmunoblastic lymphadenopathy. Blood 60:877–887.

14. Martel, P., L. Laroche, P. Courville, C. Larroche, J. Wechsler, B. Lenormand, et al. 2000. Cutaneous involvement in patients with angioimmunoblastic lymphadenopathy with dysproteinemia: a clinical, immunohistological, and molecular analysis. Arch. Dermatol. 136:881–886.

15. Zelickson, B. D., A. Tefferi, M. A. Gertz, P. M. Banks, and M. R. Pittelkow. 1989. Transient acantholytic dermatosis associated with lymphomatous angioimmunoblastic lymphadenopathy. Acta Derm. Venereol. 69:445–448.

16. Boni, R., R. Dummer, C. Dommann-Scherrer, S. Dommann, D. R. Zimmermann, H. Joller-Jemelka, et al. 1995. Necrotizing herpetic zoster mimicking relapse of vasculitis in angioimmunoblastic lymphadenopathy with dysproteinemia. Br. J. Dermatol. 133:978–982.

17. Zeligson, R., A. Yaretzky, M. Schneider, Y. Holoshitz, A. Shneur, and B. Griffe. 1981. Angioimmunoblastic lymphadenopathy in patients with angioimmunoblastic lymphadenopathy with dysproteinemia. Arch. Dermatol. 145:342–343.

18. Zhou, J., and C. Grose. 2004. Varicella and herpes zoster. Pp. 1195–1207 in L. S. Gorbach, G. J. Bartlett and R. N. Blacklow, eds. Infectious disease, 3rd ed. Lippincott Williams & Wilkins, Philadelphia.

19. Whitely, J. R. 2010. Varicella-zoster virus. Pp. 1195–1207 in L. G. Mandell, E. J. Bennett, R. Dolin, eds. Principles and practice of infectious diseases. 7th ed. Elsevier, Philadelphia.

20. Klajman, A., A. Yaretzky, M. Schneider, Y. Holoshitz, A. Shneur, and B. Griffel. 1981. Angioimmunoblastic lymphadenopathy with paraproteinemia: a T- and B-cell disorder. Cancer 48:2433–2437.

21. Dunleavy, K., W. H. Wilson, and E. S. Jaffe. 2007. Angioimmunoblastic T cell lymphoma: pathobiological insights and clinical implications. Curr. Opin. Hematol. 14:348–353.

22. Kim, S. J., D. H. Yoon, H. J. Kang, J. S. Kim, S. K. Park, H. J. Kim, et al. 2012. Bortezomib in combination with CHOP as first-line treatment for patients with stage III/IV peripheral T-cell lymphomas: a multicentre, single-arm, phase 2 trial. Eur. J. Cancer 48:3223–3231.

23. Siegert, W., A. Agthe, H. Grieser, R. Schwerdtfeger, G. Brittinger, M. Engelhard, et al. 1992. Treatment of angioimmunoblastic lymphadenopathy (AILD)-type T-cell lymphoma using prednisone with or without the COPBLAM/IMVP-16 regimen. A multicenter study. Kiel Lymphoma Study Group. Ann. Intern. Med. 117:364–370.
24. Archimbaud, E., B. Coiffier, P. A. Bryon, C. Vasselon, C. P. Brizard, and J. J. Viala. 1987. Prognostic factors in angioimmunoblastic lymphadenopathy. Cancer 59:208–212.
25. Aozasa, K., M. Ohsawa, M. Q. Fujita, Y. Kanayama, N. Tominaga, T. Yonezawa, et al. 1989. Angioimmunoblastic lymphadenopathy. Review of 44 patients with emphasis on prognostic behavior. Cancer 63:1625–1629.
26. Ch’ang, H. J., I. J. Su, C. L. Chen, I. P. Chiang, Y. C. Chen, C. H. Wang, et al. 1997. Angioimmunoblastic lymphadenopathy with dysproteinemia—lack of a prognostic value of clear cell morphology. Oncology 54:193–198.
27. Zhao, S., L. Zhang, M. Zhang, G. Yao, X. Zhang, W. Zhao, et al. 2012. Angioimmunoblastic T-cell lymphoma: the effect of initial treatment and microvascular density in 31 patients. Med. Oncol. 29:2311–2316.
28. Niino, D., Y. Komohara, T. Murayama, R. Aoki, Y. Kimura, K. Hashikawa, et al. 2010. Ratio of M2 macrophage expression is closely associated with poor prognosis for Angioimmunoblastic T-cell lymphoma (AITL). Pathol. Int. 60:278–283.
29. Wechsler, H. L., and A. Stavrides. 1977. Immunoblastic lymphadenopathy with purpura and cryoglobulinemia. Arch. Dermatol. 113:636–641.
30. Matloff, R. B., and R. S. Neiman. 1978. Angioimmunoblastic lymphadenopathy. A generalized lymphoproliferative disorder with cutaneous manifestations. Arch. Dermatol. 114:92–94.
31. Schmuth, M., J. Ramaker, C. Trautmann, M. Hummel, A. Schmitt-Graff, H. Stein, et al. 1997. Cutaneous involvement in prelymphomatous angioimmunoblastic lymphadenopathy. J. Am. Acad. Dermatol. 36:290–295.
32. Hashefi, M., T. R. McHugh, G. P. Smith, T. J. Elwing, R. W. Burns, and S. E. Walker. 2000. Seropositive rheumatoid arthritis with dermatomyositis sine myositis, angioimmunoblastic lymphadenopathy with dysproteinemia-type T cell lymphoma, and B cell lymphoma of the oropharynx. J. Rheumatol. 27:1087–1090.
33. Suarez-Vilela, D., and F. M. Izquierdo-Garcia. 2003. Angioimmunoblastic lymphadenopathy-like T-cell lymphoma: cutaneous clinical onset with prominent granulomatous reaction. Am. J. Surg. Pathol. 27:699–700.
34. Huang, C. T., and S. S. Chuang. 2004. Angioimmunoblastic T-cell lymphoma with cutaneous involvement: a case report with subtle histologic changes and clonal T-cell proliferation. Arch. Pathol. Lab. Med. 128:e122–e124.
35. Jones, B., Y. Vun, M. Sabah, and C. A. Egan. 2005. Toxic epidermal necrolysis secondary to angioimmunoblastic T-cell lymphoma. Australas. J. Dermatol. 46:187–191.
36. Tschatzis, E., D. Vassilopoulos, M. Deutsch, A. Filiotou, A. Tasidou, and A. J. Archimandritis. 2005. Angioimmunoblastic T-cell lymphoma-associated arthritis: case report and literature review. J. Clin. Rheumatol. 11:326–328.
37. Ortonne, N., J. Dupuis, A. Plonquet, N. Martin, C. Copie-Bergman, M. Bagot, et al. 2007. Characterization of CXCL13+ neoplastic t cells in cutaneous lesions of angioimmunoblastic T-cell lymphoma (AITL). Am. J. Surg. Pathol. 31:1068–1076.
38. Smithberger, E. S., D. Rezania, R. N. Chavan, M. H. Lien, H. D. Cualing, and J. L. Messina. 2010. Primary cutaneous angioimmunoblastic T-cell lymphoma histologically mimicking an inflammatory dermatosis. J. Drugs Dermatol. 9:851–855.
39. Ponciano, A., A. de Muret, L. Machet, E. Gyan, C. Monegier du Sorbier, V. Molinier-Frenkel, et al. 2012. Epidermotropic secondary cutaneous involvement by relapsed angioimmunoblastic T-cell lymphoma mimicking mycosis fungoides: a case report. J. Cutan. Pathol. 39:1119–1124.