Asian Journal of Medicine and Health Sciences Vol 4 Issue 1 June 2021

CASE REPORT

ALK-POSITIVE ANAPLASTIC LARGE CELL LYMPHOMA.

Win Myat Oo[1], Sein Win[2], Nyein Chan Aung[3]

[1]*Department of Pathology, No (1) Defence Services General Hospital, Mingalardon, Yangon, Myanmar*
[2] *Department of Clinical Haematology, Yangon General Hospital, Yangon, Myanmar*
[3] *Department of Pathology, Defence Service Medical Academy, Yangon, Myanmar*

Corresponding Author
Dr. Win Myat Oo
Department of Pathology, No (1) Defense Services General Hospital, Yangon 11021, Myanmar.
Email: winmo27@gmail.com

Abstract

The WHO 2017 revised 4th edition classifies many different types of B cell lymphomas and T and NK cells lymphomas. ALK-positive (ALK+) anaplastic large cell lymphoma (ALCL) is a T cell lymphoma consisting of large lymphoid cells which have abundant cytoplasm and pleomorphic, often horseshoe-shaped nuclei, with chromosomal translocation involving the ALK gene and expression of ALK protein and CD30. ALK+ ALCL accounts for about 5% of all non-Hodgkin lymphomas, 50% to 60% of ALCL and 10% to 15% of children's non-Hodgkin lymphomas. We present 23 years old man with single painful ulcerative growth at left buccal mucosa. The biopsy tissue shows characteristic of large cells lymphoma with the neoplastic hallmark cells. The tumour cells are positive for CD3, CD30, EMA, ALK, CD4, and TIA1. CD30 staining pattern is typically on the cell membrane and Golgi region of the neoplastic cells. ALK expression is on both nucleus ad cytoplasmic. The tumour cells are negative for CD5, CD8, CD20. Ki67 proliferation index is high, about 90% of tumour cells expressed and it matched with Anaplastic large cell lymphoma, ALK positive. Morphology is important, but immunophenotyping are also mandatory in Lymphoma diagnosis to know their specific characteristic. The precise classification of lymphoma entities has facilitated by combination of morphology, immunophenotyping and genetic features.

Key words: Non-Hodgkin Lymphoma, Anaplastic large cell lymphoma, immunophenotyping of lymphoma, ALK protein

Introduction

lymphomas are classified into two broad entities, Hodgkin lymphoma (HL) and non-Hodgkin lymphoma (NHL). ALK-positive (ALK+) anaplastic large cell lymphoma (ALCL), a subset of non-Hodgkin lymphoma, is a T cell lymphoma consisting of large lymphoid cells which have abundant cytoplasm and pleomorphic, often horseshoe-shaped nuclei, with chromosomal translocation involving the ALK gene and expression of ALK protein and CD30 [1]. ALCL with same morphologic and phenotypic features, but lacking the ALK rearrangement and the ALK protein, are considered as a separate category (ALK-negative (ALK-) ALCL) [2]. ALK+ ALCL are mainly occurred in children and young adults and has a striking male predominance, especially in the first 3 decades of life [3]. ALK+ ALCL accounts for about 5% of all non-Hodgkin lymphomas, 50% to 60% of ALCL and 10% to 15% of children's non-Hodgkin lymphomas. ALK + ALCL patients are well respond to chemotherapy with a good prognosis, whereas the ALK- ALCLs occur mostly in elderly patients (50 - 70 years) with unpredictable clinical behavior [5].

We report a case of localized ALK+ ALCL arising from buccal mucosa presented as a single painful ulcer in a 23 year-old man.

Case report

A 23-year-old man presented with single painful oral ulcer for two weeks durations and he showed to the private hospital in Yangon (shown in Fig. 1). At first, the clinician treated as aphthous ulcer but it was not cured. They took biopsy from the ulcerative growth and the first pathological diagnosis was suggestive of ulcerative diffuse high grade Non-Hodgkin lymphoma. He came to department of clinical haematology, Yangon General Hospital to show his ulcer in the mouth with his first pathological report. H&E slides were reviewed and tumour growth show proliferation of medium size to large lymphoid cells (shown in Fig. 2). They have moderate to abundant eosinophilic cytoplasm. The infiltration of histiocytes into the proliferating tumour mass makes the appearance of starry sky pattern. Most of the tumour cells have large nuclei, the nuclear chromatin is finely clumped with multiple small basophilic nucleoli. In some area, the nucleoli of some large cells show more prominent, and they are also eosinophilic. The typical hallmark cells of ALCL are also seen. These cells are large but some are small, with eccentric horseshoe-shaped nuclei are noted (shown in Fig. 3).

Based on morphology, immunohistochemical stainings of CD3, C20, CD30, EMA, CD4, CD5, CD8, ALK, TIA1, Ki67 were done. The tumour cells are positive for CD3, CD30, EMA, ALK, CD4, and TIA1 (shown in Fig. 4-9). CD30 staining pattern is typically on the cell membrane and Golgi region of the neoplastic cells. ALK expression is on both nucleus ad cytoplasmic. The tumour cells are negative for CD5, CD8, CD20. Ki67 proliferation index is high, about 90% of tumour cells expressed (shown in Fig. 10).

Based on morphology and immunophenotypic findings, this is involved by Anaplastic large cell lymphoma, ALK-positive, (ALK+ ALCL), according to the classification of WHO 2017 revised 4th edition.

Discussion

Anaplastic large cell lymphoma (ALCL) comprise primary cutaneous ALCL (CALCL) and systemic form (SALCL). ALK+ ALCL, one of SALCL forms, involves ALK gene rearrangement and expression of ALK protein and CD30. Another systemic form, ALCL with comparable morphology and phenotypic features, but lacking ALK rearrangement and ALK protein is ALK- ALCL. ALK+ ALCL frequently involves both lymph nodes and extranodal sites, of which the most commonly involved extranodal sites include the skin, bone, soft tissues, lungs and liver [1]. ALK+ ALCL is associated with a t(2;5)(p23;q35) NPM1/ALK translocation which causes the anaplastic lymphoma kinase (ALK)

gene on chromosome 2 to fuse with the NPM (nucleophosmin) gene on chromosome 5. The resulting NPM-ALK hybrid protein play a key role in lymphomagenesis by aberrant phosphorylation of intracellular substrates [3]. The recognition of t(2;5)(p23;q35) NPM1/ALK translocation made the molecular definition of a subset of ALCL tumours that harbors this translocation [4]. In lymph node involvement cases of ALK+ ALCL, systemic B-type symptoms including high fever, night sweats, and weight loss are the most common clinical presentations in about 70% to 75% of the patients but extra-nodal involvement with or without lymphadenopathy is also frequent [5].

Here in this case, the patient noticed as an painful ulcerative growth in his mouth. It was not associated with lymphadenopathy nor fever at first. He just got fever after two weeks of ulcer. He had no known history of buccal trauma. Due to non-respond treatment for aphthous ulcer, tissuse biopsy was done. Histological reviewed and limited panel of immunohistochemical stainings were done.

ALK+ ALCL is a localized or systemic advanced stage disease. Extra-nodal involvement with or without lymphadenopathy is also frequent, especially in the skin, bone, soft tissue, and lung [6].

Histologically, several morphological patterns can be recognized as common pattern (60%), lymphohistiocytic pattern (10%), small cell pattern (5- 10%), Hodgkin-like pattern (3%) and composite pattern (15%) according to WHO 2017 revised 4th edition of classification of tumours of haematopoietic and lymphoid tissues [1]. In our case, the tumour cells have abundant cytoplasm that appear eosinophilic. Most of the tumour cells have large nuclei, the nuclear chromatin is finely clumped with multiple small basophilic nucleoli. Some scattered hallmark cells are seen. This features are belong to the variant of so-called common pattern.

The morphologic features of CALCL are similar to SALCL, both containing large anaplastic lymphoid cells growing in a sinusoidal or sheet-like, cohesive pattern [7]. Unlike SALCL, CALCL expresses the cutaneous lymphocyte antigen (CLA), which determines tropism of the neoplastic cells to the skin, but does not express the epithelial membrane antigen (EMA) or ALK [8].

The hallmark of ALCL is expression of the CD30(Ki-1) molecule and positivity for CD30 is characteristically confined to the cell membrane and the Golgi region [9]. The immunophenotype of tumour cells in ALCL are CD30+, CD45+/-, CD25+/-, EMA+/-, CD15-/+, CD3-/+, CD43-/+, and CD45RO-/+ [10]. In our case, the tumour cells are positive for CD3, CD30, EMA, ALK, CD4, and TIA1. CD30 staining pattern is typically on the cell membrane and Golgi region of the neoplastic cells. CD5, CD8, CD20 were negative. Ki67 proliferation index is high, about 90% of tumour cells expressed.

Most ALK+ ALCL are positive for EMA [11] and in our case tumour cells expressed EMA and ALK on both nucleus and cytoplasmic. This is different in CALCL, in which tumour cells are negative for EMA. In most cases of ALCL that have t(2;5)(p23;q35) NPM1/ALK translocation, ALK staining of large cells is both cytoplasmic and nuclear staining according to the studies [11-13]. Most cases of ALK+ ALCL show positivity for T cell cytotoxic antigens [14]. CD4 is expressed in most cases and CD8 is in a minor subset (19%) of ALK+ALCL in the study of Jing Shen et al [15]. In our case, tumour cells express CD4, TIA1 but it is negative for CD8.

ALK+ ALCL has favorable prognosis [16]. In the studies of Williams DM et al and Zinzani PL et al, the response of ALCL to chemotherapy is desirable and the remission rate ranges from 60%-90% [17,18]. In the study of Brugières L et al, nearly 90% of patients with ALK+ ALCL treated with anthracycline-based chemotherapy achieve a tumour response, with 60% of patients remaining relapse free at 5 years [19].

Conclusion

In conclusion, ALK+ ALCL can present as a single painful ulcerative growth. In daily clinical practice, lymphoma is the main differential diagnosis when it involved in skin and oral mucosa. Thorough clinical examination, histologic evaluation combined with immunohistochemistry make an accurate diagnosis of ALK+ ALCL. Suitable chemotherapy can be given when the diagnosis is confirmed.

Conflict of Interest

The authors declare no conflict of interest.

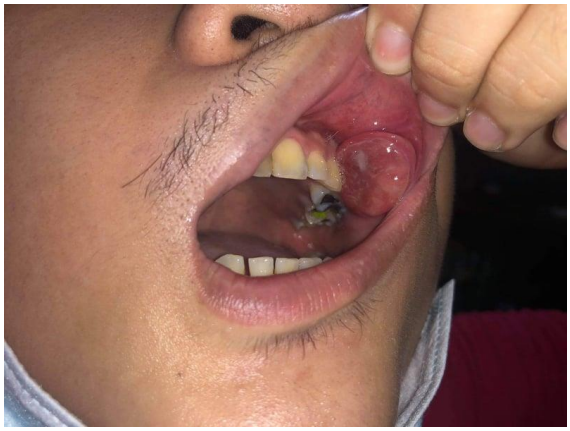

Figure 1. Ulcerative growth at left buccal mucosa in a 23-year-old man.

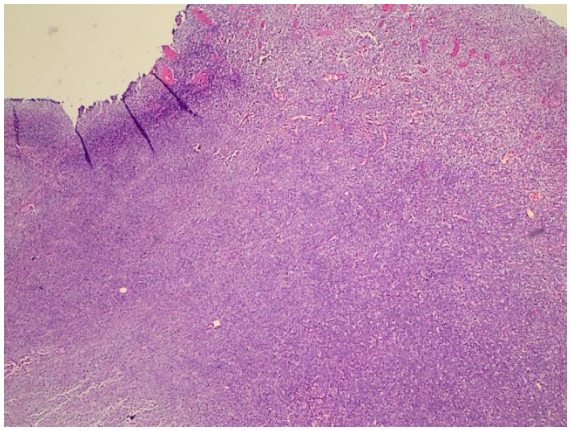

Figure 2. Dense infiltrate of medium size to large lymphoid cells in the lesion of buccal mucosa (H&E, 10x).

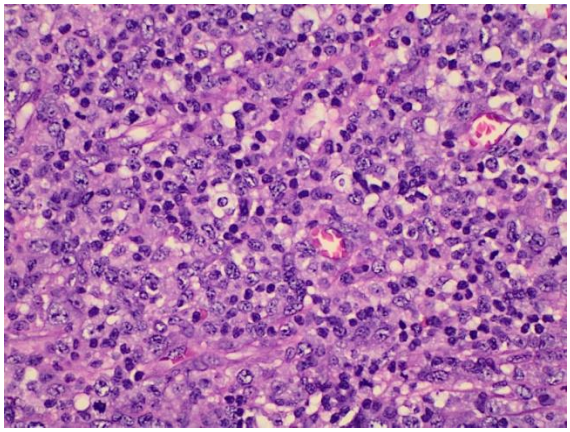

Figure 3. Anaplastic large cell lymphoma, predominant population of large cells with irregular nuclei, have eosinophilic cytoplasm. Some scattered large and small cells showing eccentric kidney-shaped nuclei are so- called hallmark cells (H&E, 40x).

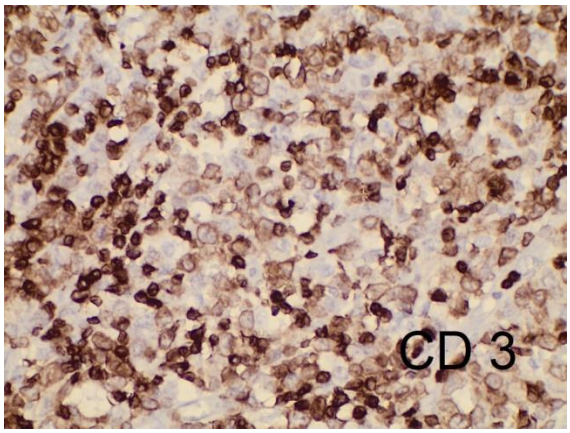

Figure 4. CD3 expression is faintly positive in large tumour cells.

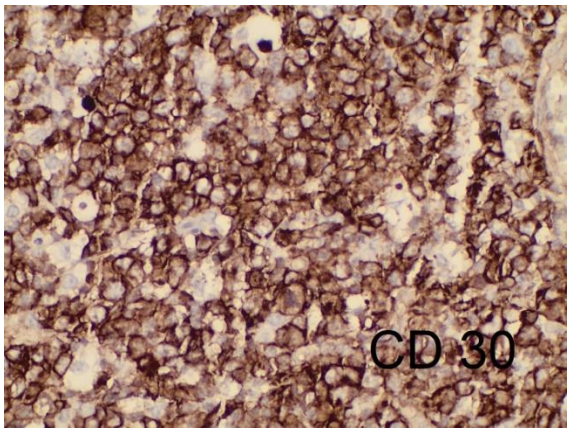

Figure 5. CD30 expression in tumour cells.

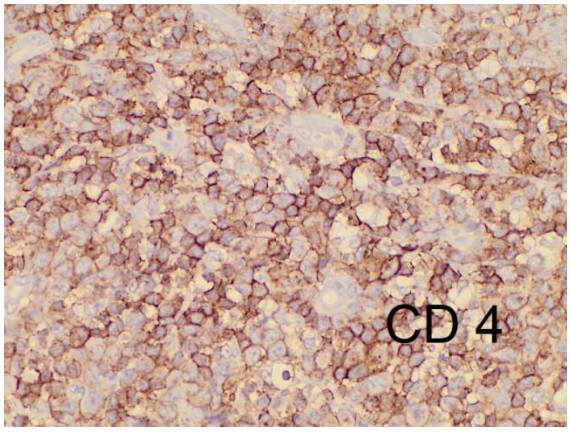

Figure 6. CD4 expression was seen in tumour cells.

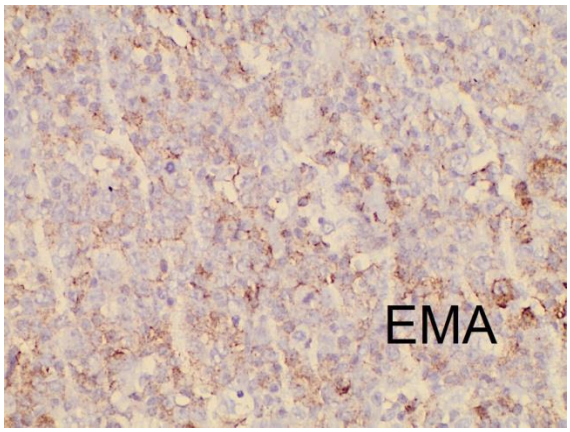

Figure 7. Most ALK+ ALCL cells are positive for EMA.

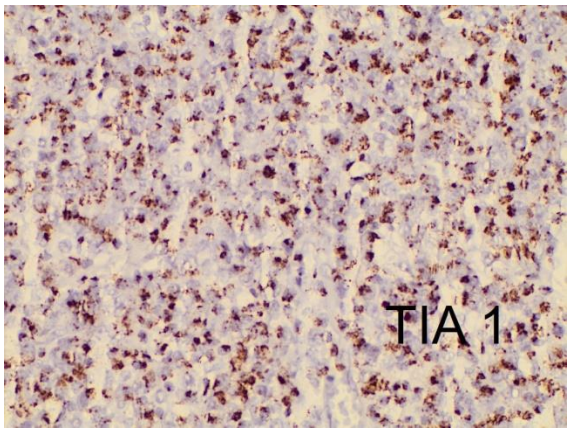

Figure 8. Tumour cells exhibit positivity for the cytotoxic antigen, TIA1.

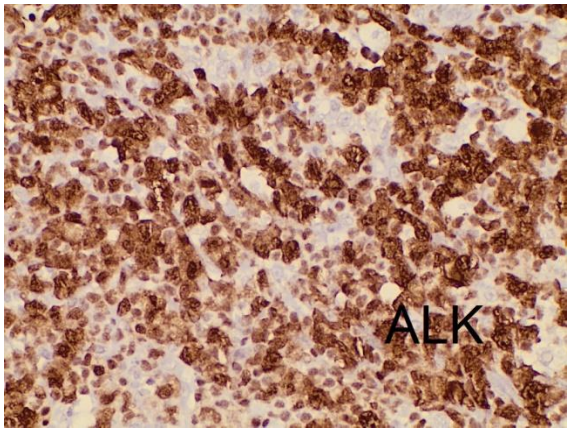

Figure 9. ALK staining of large neoplastic cells is both nuclear and cytoplasmic patterns.

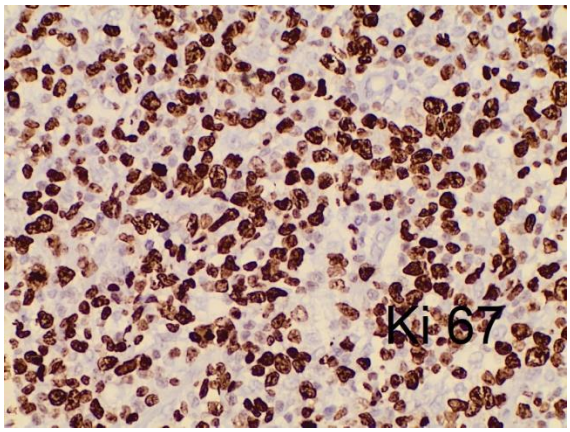

Figure 10. High Ki67 proliferation about 90% of tumour cells.

References

1. 1. Swerdlow SH, Campo E, Harris NL, Jaffe ES, Pileri SA, Stein H, Thiele J. WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues. Revised 4th ed. Lyon, France: IARC Press, 2017; pp. 413–414.
2. Ferreri A J, Govi S, Pileri S A, Savage K J. Anaplastic large cell lymphoma, ALK-positive: Critical Reviews in Oncology/Hematology 83 (2012) 293–302.
3. Falini B, Pileri S, Zinzani PL, Carbone A, Zagonel V, Wolf-Peeters C, et al. ALK+ lymphoma: Clinico-pathological findings and outcome. Blood. 1999;93(8):2697–706.
4. Amin HM, Lai R. Pathobiology of ALK+ anaplastic large-cell lymphoma. Blood. 2007;110(7):2259-67.

5. Fatemeh Nili, Vahid Soleimani, Niusha Nobari, Hana Saffar and Arghavan Etebarian: ALK Positive Anaplastic Large Cell Lymphoma of Oral Cavity: A Case Report. Int J Cancer Manag. 2019 January; 12(1): e85749.

6. Joel B. Epstein, Joshua D. Epstein, Nhu D. Le, and Meir Gorsky: Characteristics of oral and paraoral malignant lymphoma: A population-based review of 361 cases. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2001; 92: 519-25.

7. Sarah G Fitzpatrick 1, Leah M Bowers 2, Samer Z Al-Quran 3, Eric G Fox 4, Donald M Cohen 2, Indraneel Bhattacharyya. ALK negative anaplastic large cell lymphoma of the oral cavity showing spontaneous regression. Journal of Hematological Malignancies, June 2012, Vol. 2, No. 2:49-56.

8. Thiago Jeunon de Sousa Vargas, Samira Barroso Jorge and Yung Bruno de Mello Gonzaga: CD30-positive cutaneous lymphoma: report of four cases with an emphasis on clinicopathological correlation. An Bras Dermatol. 2017;92(1):86-91.

9. Brunangelo Falini: Anaplastic large cell lymphoma: pathological, molecular and clinical features; BJHeam, 20 December 2001, Vol 114, Issue 4,741-760.

10. Ken-ichi Notani, Masanobu Shindoh, Tsuyoshi Takami, Yutaka Yamazaki, Takao kohgo, and Hiroshi Fukuda. Anaplastic large cell lymphoma (ALCL) in the oral mucosa with repeating recurrence and spontaneous regression of ulceration: report of a case. Oral Med pathol 7(2002).79- 82.

11. Benharroch D, Meguerian-Bedoyan Z, Lamant L, et al. ALK-positive lymphoma: A Single Disease with a Broad Spectrum of Morphology. April 1998. Blood 91 (6):2076-84.

12. Falani B, Bigerna B, Fizzoti M, Pulford K, Pileri S A, Delson G, et al. ALK expression defines a distinct group of T/null lymphomas ("ALK Lymphomas") with a wide morphological spectrum. Am J Pathol. 1998 Sept :153 (3) :875-876.

13. Stein H, Foss HD, Dürkop H. CD30(+) anaplastic large cell lymphoma: a review of its histopathologic, genetic, and clinical features. Blood 2000;96(December (12)):3681–95.

14. Foss HD, Anagnostopoulos I, Araujo I, Assaf C, Demel G, Kumma A J et al. Anaplastic large cell lymphomas of T cell and null cell phenotype express cytotoxic molecules. Blood 1996 Nov15;88 (10):4005-11.

15. Jing Shen, L Jeffrey Medeiros, Shaoying Li, Sa A Wang, Pei Lin, Mahsa Khanlari et al. CD8 expression in anaplastic large cell lymphoma correlates with noncommon morphologic variants and T cell antigen expression suggesting biological differences with CD8-neative anaplastic large cell lymphoma. Hum Pathol. 2020 Apr; 98: 1-9.

16. Yuan Yang, Qibing Xie, Yi Liu, Yuehong Chen, Geng Yin. ALK-positive anaplastic large cell lymphoma with multifocal bone involvements: a case report and review of the literature. Int J Clin Exp Med 2018;11(3):2745-2751.

17. Williams DM, Hobson R, Imeson J, Gerrard M, McCarthy K, Pinkerton CR; United Kingdom Children's Cancer Study Group. Anaplastic large cell lymphoma in childhood:

analysis of 72 patients treated on the United Kingdom children's cancer study group chemotherapy regimens. Br J Haematol 2002; 117: 812-820.

18. Zinzani PL, Martelli M, Magagnoli M, Zaccaria A, Ronconi F, Cantonetti M, Bocchia M, Marra R, Gobbi M, Falini B, Gherlinzoni F, Moretti L, De Renzo A, Mazza P, Pavone E, Sabattini E, Amendola A, Bendandi M, Pileri SA, Mandelli F and Tura S. Anaplastic large cell lymphoma Hodgkin's-like: a randomized trial of ABVD versus MACOP-B with and without radiation therapy. Blood 1998; 92: 790-794.

19. Brugières L, Quartier P, Le Deley MC. Relapses of childhood anaplastic large-cell lymphoma: treatment results in a series of 41 children—a report from the French Society of Pediatric Oncology. Ann Oncol 2000;11(January (1)):53–8.