Effusion-associated anaplastic large cell lymphoma of the breast: time for it to be defined as a distinct clinico-pathological entity

Anaplastic large cell lymphoma (ALCL) can present with systemic disease or disease limited to the skin.[1] Systemic ALCL is an aggressive disease, with advanced stage disease, B symptoms and extra-nodal disease commonly seen at presentation. ALCL can be subdivided according to the expression of Anaplastic Lymphoma Kinase (ALK),[2] detectable immunohistochemically in 51-60% of cases.[3,4] ALK expression is associated with chromosomal translocations, most commonly t(2;5), which creates an *ALK-NPM* fusion gene.[3] ALK-positive disease is more common in younger patients and is associated with a superior prognosis, with 5-year overall survival of 71-79% compared to 15-46% in ALK-negative cases.[3,4] Strong, uniform CD30 expression is a hallmark of ALCL, as distinct from peripheral T-cell lymphoma, not otherwise specified (PTCL, NOS), where staining is present in a proportion of cells and of variable intensity. Primary cutaneous ALCL is always ALK negative and typically presents with solitary or localized nodules or tumors. It has a superior prognosis, with a 5-year survival beyond 90%. Treatment with surgical excision or local radiotherapy alone generally results in long-term survival.[5]

Thirty-one cases of extra-nodal CD30$^+$ ALCL limited to the breast have now been described, 23 occurring in association with either saline and silicone implants, implanted for both cosmetic reasons and for breast reconstruction post-breast cancer surgery.[6-10] A large, population-based study from the Netherlands has recently suggested an association between ALCL and breast prostheses.[7] In contrast, five epidemiological studies, ranging in size from 2,171 to 24,558 patients (median 6,222), which have followed cohorts of women with breast implants, have not shown an increased lymphoma risk.[11] The lack of strong epidemiological evidence makes a firm conclusion regarding the causative role of breast implants in this disease more difficult. Nevertheless, we believe there is strong clinical and pathological evidence for a causative role and the current lack of corroborative epidemiological data most likely reflects the extreme rarity of the disease. Recently, it has been suggested that there is a potential association between ALCL and textured (rather than non-textured) breast implants.[12] A co-operative American Plastic Surgical group are currently undertaking a prospective assessment of the overall risk (*www.plasticsurgery.org*).

NHL of the breast is very rare, with lymphoma involving the breast accounting for approximately 0.04-0.5% of malignant breast tumors and 2.2% of extra-nodal lymphomas.[13] Furthermore, more than 90% of these are of B-cell lineage. Of the less than 10% which are of T-lineage, most are peripheral T-cell lymphoma, not otherwise specified (PTCL-NOS).[8] If the association between lymphoma and breast implants were purely co-incidental, one would expect the ratio of B-cell to T-cell lymphomas to be similar to that observed in women without implants, namely greater than nine to one. In fact, the ratio is reversed; of the more than 31 reported cases of primary breast lymphoma in close proximity to breast implants, only 3 are of B-cell origin.[8]

In addition to the likely etiological association, we and others[8] believe that there is compelling evidence that primary ALCL arising in close proximity to breast implants represents a distinct clinico-pathological entity. Women with breast involvement as part of *systemic* ALCL typically present with a mass lesion. In contrast, women with breast implants generally present with implant-related symptoms, most commonly an effusion in the absence of a mass lesion (n=10). Roden *et al.* call this "seroma-associated primary anaplastic large cell lymphoma."[8] We would suggest the term "effusion-associated anaplastic large cell lymphoma" (ea-ALCL) given that the fluid is a malignant effusion rather than serum. In the 4 cases they describe, effusion aspirate specimens showed aggressive cytological features similar to those of systemic ALCL. Immunophenotypically, they were indistinguishable, with CD30 positivity and a T-cell phenotype, evidenced by CD3 and CD4 expression. Malignancy was confirmed by the presence of monoclonal TCR rearrangements and/or the demonstration of phenotypic aberrancy, including CD4 and CD8 co-expression. However, despite this, on histological examination of resected specimens, there was no evidence of tissue invasion, with lymphoma cells suspended in a serous/fibrinous background adjacent to the peri-implant capsule (Figure 1).

An illustrative case was recently observed at our institution. The patient, a 45-year old woman who had had cosmetic breast implants performed for congenital breast

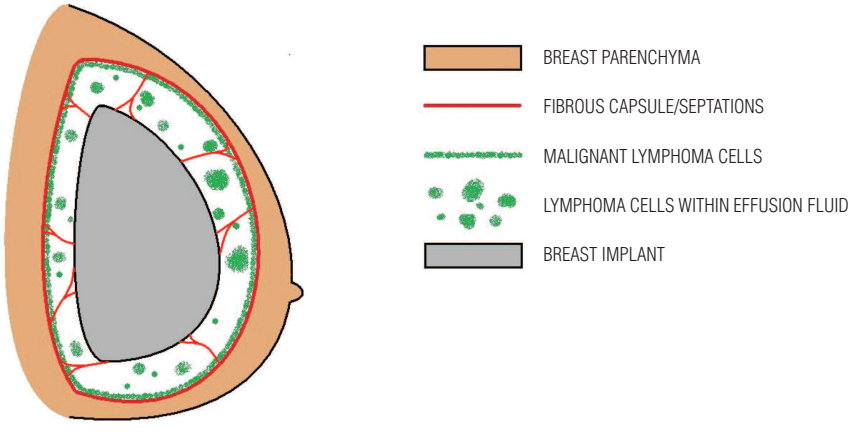

Figure 1. Schematic representation of effusion-associated anaplastic large cell lymphoma. The septated effusion is contained between the implant and the fibrous capsule which surrounds the implant. The malignant cells are contained within the effusion fluid and adherent to the fibrous capsule, within a sero-fibrinous exudate. There is no invasion beyond the fibrous capsule into the breast parenchyma.

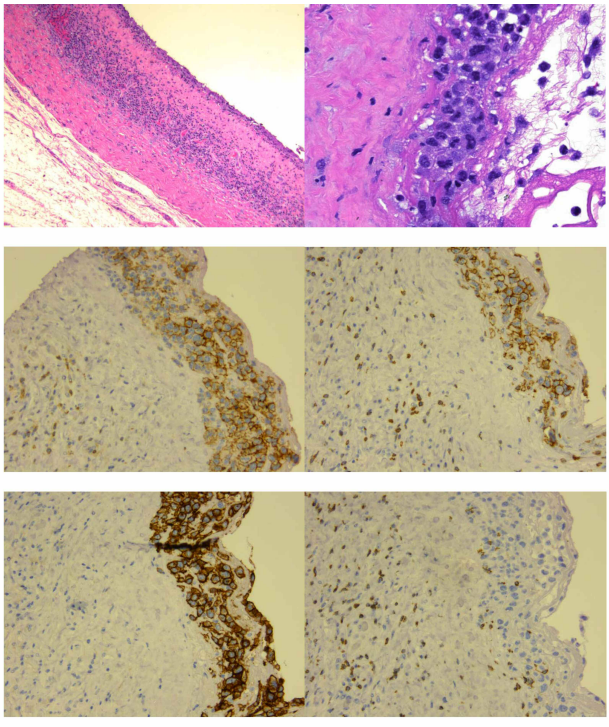

Figure 2. Top row – H&E x 40 and x 200 showing fibrous capsule and tumor cells within a sero-fibrinous exudate. Middle row: CD4 and CD8 at x 100, showing aberrant co-expression. Lower row: CD30 at x 100, showing strong membrane staining of the tumor, with no invasion into tissue. CD2 at x 100, showing aberrant loss of staining of tumor cells.

hypoplasia, presented with an effusion four years after initial implantation. She subsequently underwent *en bloc* surgical removal of the intact saline implant and surrounding fibrous capsule six months after initial presentation. Histological examination revealed a pleomorphic infiltrate of large cells, suspended in a sero-fibrinous exudate adjacent to, but not invading the fibrous capsule (Figure 2). Moreover, a unique cell-line (TLBR-1) was created from cells cultured from the aspirated fluid, which is the first such line and closely recapitulates the clinical disease. The precise mechanism of lymphomagenesis in this condition is not clear. It has been shown that small amounts of silicone leak into surrounding tissues even when the capsule of the implant is intact; intracellular silicone can be found in macrophages within the reactive fibrovascular capsule that surrounds the implant. Additionally, saline implants are surrounded by an impermeable silicone elastomeric capsule.[8] Silicone is immunogenic and has been shown to induce plasmacytomas in genetically predisposed mice.[8] It is possible that chronic antigenic stimulation of T cells by silicone may be capable of inducing lymphoma in these rare cases. Hopefully, investigation of the TLBR-1 cell line will lead to further insights into the pathogenesis of this condition.

Of the 23 implant-associated cases of primary breast ALCL, the presenting clinical features are known in 18 and were heterogenous, most commonly peri-implant effusion (n=10), ranging in volume from 200-720mL. All patients were female, with a median age of 47 (24-87). Implants were performed for cosmetic reasons in 14 women and for breast reconstruction after surgery for breast cancer in 8. The reason was unknown in one. ALCL developed after a median time of seven years post-implant (range 1-23 years). All patients had surgical removal of the implant. Post-surgical treatment has been heterogeneous, including radiotherapy alone, combination chemotherapy, and combined chemotherapy and radiation. One patient[8] declined post-surgical treatment and has not relapsed after 20 months of follow up. Eleven of 12 patients with follow-up details available are alive and disease-free.

The evidence to date clearly supports the contention that, unlike systemic ALCL, ea-ALCL is an indolent condition, with clinical behavior more analogous to primary cutaneous ALCL.[8] However, follow up of patients is of limited duration, with a median follow up of 12 months (range 4–40 months) and longer follow up is required before we can confirm that these tumors behave in a truly indolent fashion. Intriguingly, the only patient known to have relapsed after treatment presented with a mass lesion, suggesting that in this single case,[6] the pathobiology of the disease may have been different to those presenting with effusion alone. Taken together, we feel that ea-ALCL will not fit into the category of systemic ALK-negative ALCL and warrants its own separate categorization in the WHO classification.

Data on treatment modalities and outcomes is limited and evidence-based recommendations for treatment of an individual patient presenting with ea-ALCL cannot be made. However, given that the clinico-pathological features are most similar to primary cutaneous ALCL, we believe that it is most appropriate to treat patients with localized ea-ALCL along a similar paradigm to patients with cutaneous ALCL. In particular, aggressive systemic chemotherapy is likely unnecessary. However, when a patient presents with implant-associated ALCL where effusion is not the mode of presentation, particularly where there is a mass lesion, it is less certain that their disease will behave in an indolent fashion and more aggressive treatment may be appropriate. Given the lack of data, treatment decisions need to be individualized.

Philip A. Thompson,[1] Stephen Lade,[2] Howard Webster,[3] Gail Ryan,[4,5] H. Miles Prince[1,5]

[1]Dept. Haematology, Peter MacCallum Cancer Centre, Melbourne, Australia; [2]Dept. Pathology, Peter MacCallum Cancer Centre; [3]ARC Plastic Surgery, Victoria, Australia; [4]Division of Radiation Oncology, Peter MacCallum Cancer Centre; [5]University of Melbourne, Parkville, Victoria, Australia

Correspondence: H. Miles Prince, DHMO, Peter MacCallum Cancer Centre, Locked Bag 1, A'Beckett St Melbourne, Victoria, 8006, Australia. Fax: internatioanal +61.3.96561700. E-mail: Miles.prince@petermac.org

Key words: lymphoma, anaplastic, CD30, breast, effusion.

Citation: Thompson PA, Lade S, Webster H, Ryan G, Prince HL. Effusion-associated anaplastic large cell lymphoma of the breast: time for it to be defined as a distinct clinico-pathological entity. Haematologica 2010; 95(11):1977-1979 doi:10.3324/haematol.2010.026237

References

1. Swerdlow SH, Campo E, Harris NL, Jaffe ES, Pileri S, Stein H, et al, ed. WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues. 4th ed. Lyon: International Agency for Research on Cancer, 2008.
2. Falini B, Martelli MP. Anaplastic large cell lymphoma: changes in the World Health Organization classification and perspectives for targeted therapy. Haematologica. 2009;94(7):897-900.
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. Gascoyne RD, Aoun P, Wu D, Chhanabhai M, Skinnider BF, Greiner TC, et al. Prognostic significance of anaplastic lymphoma kinase (ALK) protein expression in adults with anaplastic large cell lymphoma. Blood. 1999;93(11):3913-21.
5. Willemze R, Jaffe ES, Burg G, Cerroni L, Berti E, Swerdlow SH, et al. WHO-EORTC classification for cutaneous lymphomas. Blood. 2005;105(10):3768-85.
6. Gaudet G, Friedberg JW, Weng A, Pinkus GS, Freedman AS. Breast lymphoma associated with breast implants: two case-reports and a review of the literature. Leuk Lymphoma. 2002;43(1):115-9.
7. de Jong D, Vasmel WL, de Boer JP, Verhave G, Barbe E, Casparie MK, et al. Anaplastic large-cell lymphoma in women with breast implants. JAMA. 2008;300(17):2030-5.
8. Roden AC, Macon WR, Keeney GL, Myers JL, Feldman AL, Dogan A. Seroma-associated primary anaplastic large-cell lymphoma adjacent to breast implants: an indolent T-cell lymphoproliferative disorder. Mod Pathol. 2008;21(4):455-63.
9. Li S, Lee AK. Silicone implant and primary breast ALK1-negative anaplastic large cell lymphoma, fact or fiction? Int J Clin Exp Pathol. 2009;3(1):117-27.
10. Miranda RN, Lin L, Talwalkar SS, Manning JT, Medeiros LJ. Anaplastic large cell lymphoma involving the breast: a clinicopathologic study of 6 cases and review of the literature. Arch Pathol Lab Med. 2009;133(9):1383-90.
11. Lipworth L, Tarone RE, McLaughlin JK. Breast implants and lymphoma risk: a review of the epidemiologic evidence through 2008. Plast Reconstr Surg. 2009;123(3):790-3.
12. Brody G, Deapen D, Gill P, Epstein A, Martin S, Elatra W. T-cell non-Hodgkins anaplastic lymphoma associated with one style of breast implants. 2010 [Available from: http://www.aaps1921.org/abstracts/2010/4.cgi
13. Cohen PL, Brooks JJ. Lymphomas of the breast. A clinicopathologic and immunohistochemical study of primary and secondary cases. Cancer. 1991;67(5):1359-69.

Highly active antiretroviral therapy alone may be an effective treatment for HIV-associated multicentric Castleman's disease

Multicentric Castleman's disease (MCD) is a rare lymphoproliferative disorder mainly seen in HIV-infected patients and associated with poor prognosis. Pre-HAART mortality was 70-85%.[1] Proliferation of polyclonal but often monotypic plasmablastic cells is thought to be driven by Kaposi sarcoma herpes virus (KSHV) infection, present in all patients with HIV-associated MCD.[2] There is no standard treatment. Interventions include rituximab, lymphoma-type treatment with chemotherapy and splenectomy,[1,3-7] Many are used concomitantly making it difficult to ascertain which is of greatest efficacy.

We describe 4 cases of biopsy-proven HIV-associated MCD who showed a complete clinical and radiological response to MCD, and a reduction in KSHV viral load to HAART alone without additional therapeutic interventions. All patients are alive and relapse free 19-38 months later.

Between February 1st 2007 and October 1st 2008, we identified 4 consecutive patients who received HAART alone for lymph node biopsy-proven HIV associated-MCD (Table 1). Median duration of HIV infection prior to MCD was two years (range 1-14). In all patients, nodes showed a mixture of reactive lymphoid follicles and follicles with irregular, regressed germinal centers. At the periphery of these regressed germinal centers were large plasmablastic cells with prominent nucleoli and basophilic cytoplasm, usually CD20 negative, and showing positive staining for KSHV, IgM and lambda light chains (Figure 1). All patients presented with fever, lymphadenopathy, hepatosplenomegaly and elevated C-reactive protein (CRP). Three patients investigated with FDG PET/CT scan showed FDG avid lymphadenopathy above and below the diaphragm. Three patients had started HAART less than 3-5 weeks before presentation with MCD; HAART had been initiated due to a combination of CD4 decline and constitutional symptoms. HAART was modified in one patient and interrupted in one patient due to renal and liver impairment. In all patients, resolution of constitutional symptoms occurred within three months of starting HAART. Patient 2 had a recrudescence of symptoms (fever, splenomegaly and elevated CRP) eight months after diagnosis of MCD which resolved spontaneously. Serum KSHV was 6,600 copies/mL during this flare. Three months previously KSHV had been 3,600 copies/mL. Three patients who initially demonstrated significant FDG avid lymphadenopathy now showed complete metabolic response on repeat PET/CT scan and the remaining patient CRu on repeat whole body CT scan. At time of MCD diagnosis, all samples from patients were positive for KSHV between 420 and 120,000 copies/mL; 3 patients had sustained undetectable KSHV viral loads following antiretroviral therapy. KSHV was detectable in 2 patients in whom retrospective sampling of stored blood was avail-

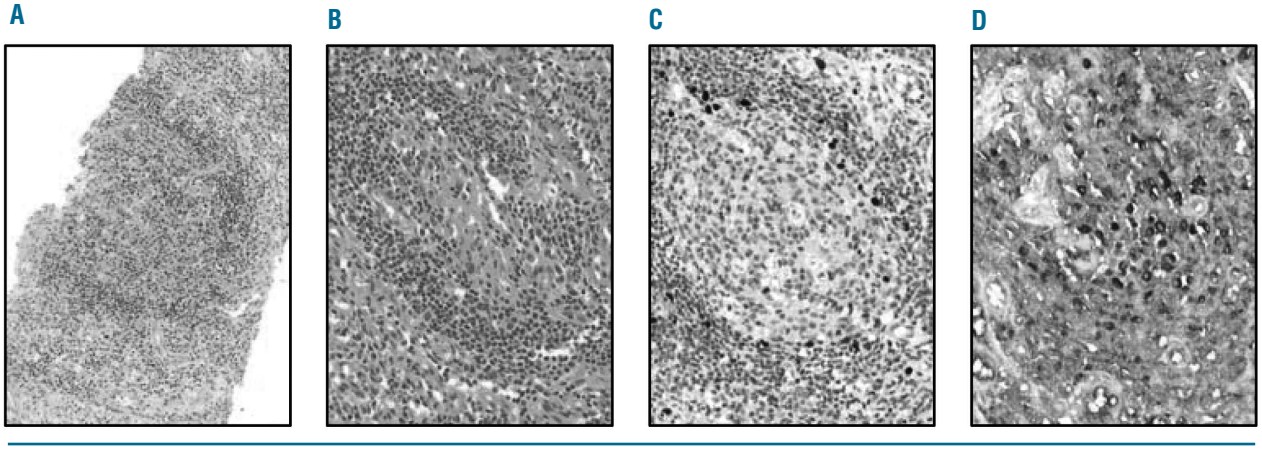

Figure 1. Composite histological figure showing features of MCD in lymph node biopsy. (A) Routine Hematoxylin and Eosin (H&E) section of a needle core biopsy of node showing an abnormal germinal center with irregular outline and scattered large plasmablastic cells (x110 original magnification). (B) High power H&E from a whole node biopsy showing a characteristic regressed germinal center with plasmablastic cells (x220 original magnification). (C) KSHV immunohistochemistry showing a target-like arrangement of KSHV-positive plasmablasts around a germinal center. (D) Lambda light chain immunohistochemistry showing cytoplasmic positivity in the plasmablastic cells in a germinal center.