

Plasma cells in classical Hodgkin lymphoma: a new player in the microenvironment?

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Classical Hodgkin lymphoma (cHL) is one of the most common malignancies affecting young adults and has a good prognosis in this group. The unusual composition of cells in cHL, consisting of less than 1% of tumour cells and 99% of reactive infiltrate, has intrigued scientists for a long time. The microenvironment in cHL is now thought to produce survival signals as well as serve as a physical barrier against immune responses. The tumour cells however, largely determine which cells are attracted to the affected lymph node by producing several chemokines and cytokines and, in addition, actively suppress an immune response by the production of suppressive factors, expression of inhibitory immune checkpoints and the loss of human leucocyte antigen (HLA) expression (Liu *et al*, 2014). In the last 2 decades, the role of the microenvironment, particularly its composition, has become increasingly important in the prognosis of cHL. This includes increased numbers of eosinophils (Enblad *et al*, 1993), mast cells (Molin *et al*, 2002), T regulatory cells (Hollander *et al*, 2017) and macrophages (Steidl *et al*, 2010), all of which cause a worse prognosis. So far, this has not affected treatment decisions.

A new paper (Gholiha *et al*, 2019) in this issue of the British Journal of Haematology, explored the role of plasma cells in the survival and clinical parameters of cHL. This study investigated a more recent Swedish patient cohort of 120 patients, collected within 3 years and with uniform modern treatment. These patients have been used for other studies in the past and several data on other parameters were available for comparison with the newly collected data. Tissue biopsies were stained for CD138 and IgG4 and scored by both digital analysis and manual scoring. Plasma cell infiltration ($\geq 1\%$) was found in 70 out of 120 patients, while high plasma cell infiltration ($\geq 10\%$) was found in 8

patients. High plasma cell infiltration was associated with B-symptoms, advanced stage, eosinophil numbers and inferior survival.

That plasma cells are associated with B symptoms and have a role in the prognosis of cHL is new. The particular strength of this paper is the patient cohort, which has been treated uniformly and according to recent protocols.

What we still need to figure out is how do plasma cells access the microenvironment and whether there is a role for plasma cells in cHL.

In cHL, plasma cells can be attracted by CCL28 or the presence of cytokines, such as interleukin IL-6 and IL-21, can play a role in the differentiation of plasma cells. Both CCL28 and the interleukins are produced by the Hodgkin and Reed–Sternberg cells in cHL. CCL28 is produced in approximately 80% of HL cases (Hanamoto *et al*, 2004) and also attracts eosinophils, which would fit with their increased numbers. Serum levels of IL-6 are indeed associated with B-symptoms (Gaiolla *et al*, 2011), and high levels (>30 pg/ml) are found in 23% of HL cases (Casasnovas *et al*, 2007). It is interesting to correlate IL-6 and CCL28 levels with the presence of plasma cells in the microenvironment to answer the first part of the question. Is there a role for plasma cells in cHL is more difficult to answer, as we have no clues regarding which factors these cells produce that are advantageous in any way for tumour cells. For now, we should consider them as a by-product of the large number of factors produced by the tumour cells in cHL.

Do B-symptoms (night sweats, fever and/or weight loss) need to be treated? So far, it seems that the tumour cells themselves are responsible for these symptoms, so eliminating the tumour cells usually affects the B-symptoms as well. Will this finding affect the way clinicians treat their patients? Not very likely – although an effective and easy to implement tool that would predict the effect of treatment is really needed. This is especially important in young adults, where the long-term effects of a harsh treatment can be felt and should be prevented when possible. None of the markers produced so far are robust enough to use, including the newly reported plasma cells.

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What we can learn from this paper is that plasma cells play a role in the microenvironment of cHL next to macrophages, eosinophils and T regulatory cells. In addition, high numbers of plasma cells may cause B-symptoms and have an

inferior effect on prognosis. This will not lead to changes in the treatment of cHL directly, but our image of the microenvironment is more complete and will contribute to the use of therapies tackling the microenvironment in cHL.

References

- Casasnovas, R.-O., Mounier, N., Brice, P., Divine, M., Morschhauser, F., Gabarre, J., Yves, J.-Y., Voillat, L., Lederlin, P., Stamatoullas, A., Bienvenu, J., Guiguet, M., Intrator, L., Grandjean, M., Briere, J., Ferme, C. & Salles, G. (2007) Plasma cytokine and soluble receptor signature predicts outcome of patients with classical Hodgkin's lymphoma: a study from the Groupe d'Etude des Lymphomes de l'Adulte. *Journal of Clinical Oncology*, **25**, 1732–1740.
- Enblad, G., Sundstrom, C. & Glimelius, B. (1993) Infiltration of eosinophils in Hodgkin's disease involved lymph nodes predicts prognosis. *Hematological Oncology*, **11**, 187–193.
- Gaiolla, R.D., Domingues, M.A.C., Niero-Melo, L. & de Oliveira, D.E. (2011) Serum levels of interleukins 6, 10, 13 before and after treatment of classic Hodgkin lymphoma. *Archives of Pathology and Laboratory Medicine*, **135**, 483–489.
- Gholiha, A., Hollander, P., Hedstrom, G., Sundstrom, C., Molin, D., Smedby, K., Hjalgrim, H., Glimelius, I., Amini, R.-A. & Enblad, G. (2019) High tumour plasma cell infiltration reflects an important microenvironmental component in classic Hodgkin lymphoma linked to presence of B-symptoms. *British Journal of Haematology*, in press.
- Hanamoto, H., Nakayama, T., Miyazato, H., Takegawa, S., Hieshima, K., Tatsumi, Y., Kanamaru, A. & Yoshie, O. (2004) Expression of CCL28 by Reed-Sternberg cells defines a major subtype of classical Hodgkin's disease with frequent infiltration of eosinophils and/or plasma cells. *American Journal of Pathology*, **164**, 997–1006.
- Hollander, P., Rostgaard, K., Smedby, K.E., Molin, D., Loskog, A., de Nully Brown, P., Enblad, G., Amini, R.-A., Hjalgrim, H. & Glimelius, I. (2017) An anergic immune signature in the tumor microenvironment of classical Hodgkin lymphoma is associated with inferior outcome. *European Journal of Haematology*, **100**, 88–97.
- Liu, Y., Sattarzadeh, A., Diepstra, A., Visser, L. & van den Berg, A. (2014) The microenvironment in classical Hodgkin lymphoma: an actively shaped and essential tumor component. *Seminars Cancer Biology*, **24**, 15–22.
- Molin, D., Edström, A., Glimelius, I., Glimelius, B., Nilsson, G., Sundström, C. & Enblad, G. (2002) Mast cell infiltration correlates with poor prognosis in Hodgkin's lymphoma. *British Journal of Haematology*, **119**, 122–124.
- Steidl, C., Lee, T., Shah, S.P., Farinha, P., Han, G., Nayar, T., Delaney, A., Jones, S.J., Iqbal, J., Weisenburger, D.D., Bast, M.A., Rosenwald, A., Muller-Hermelink, H.K., Rimsza, L.M., Campo, E., Delabie, J., Braziel, R.M., Cook, J.R., Tubbs, R.R., Jaffe, E.S., Lenz, G., Connors, J.M., Staudt, L.M., Chan, W.C. & Gascoyne, R.D. (2010) Tumor-associated macrophages and survival in classical Hodgkin's lymphoma. *New England Journal of Medicine*, **362**, 875–885.