Human Leukocyte Antigen (HLA) expression and Immunological Events in Chondrosarcoma

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Background: Chondrosarcoma are among the most prevalent primary orthopedic bone tumors. Chondrosarcoma are potentially lethal, especially regarding the higher grade and dedifferentiated chondrosarcoma. Currently the treatment for chondrosarcoma relies predominantly on surgical resection since the effect of other treatments, such as chemotherapy and radiation therapy, is limited. Therefore new and more effective treatment options are needed. In finding new therapies in the treatment of cancer, the interest in the use of immunotherapies has been revived. The role of the host immune system in preventing cancer as well as its influence on the course of the disease have been known for many years.

Questions/purposes: The aim of this study is to investigate the immunological properties and opportunities for immunotherapy in chondrosarcoma. The purpose was to assess the expression of HLA class I, HLA class II and the presence of tumor infiltrating T lymphocytes in conventional and dedifferentiated chondrosarcoma.

Patients and Methods: We developed a database and corresponding tissue microarray of patients treated surgically for chondrosarcoma at our institution over the past 20 years for both conventional and dedifferentiated chondrosarcoma. Patients that had a histological confirmed diagnosis of a non-cranial bony conventional or dedifferentiated chondrosarcoma, initial resection performed at our institution and a minimum follow-up of at least 2 years (or until death) were included. This resulted in our database and corresponding tissue microarray of 76 patients; 24 of them were diagnosed with a dedifferentiated chondrosarcoma. For the patients who survived their chondrosarcoma the mean follow-up was 7.8 ± 4.2

years (range, 2.0-19). The mean age in the entire cohort was 56 years (range 18-83) and 51% of the patients were male patients.

Our tissue microarray was stained with HLA-specific monoclonal antibodies (mAbs) utilizing the immunoperoxidase-staining technique.

Results: HLA-A, HLA-BC, B2m and HLA-II expression was downregulated in all grade 1, 2 and 3 conventional chondrosarcoma (100%) (all tumors show a mean expression of less than 90% of the cells). In the dedifferentiated chondrosarcoma the percentage of tumors being downregulated in HLA-A, HLA-BC, B2m and HLA-II expression was downregulated in 48%, 9.5%, 85% and 86% of the tested tumors, respectively.

High-grade conventional chondrosarcoma (grade 2 and 3) express more HLA-A (39% vs. 16%, P=0.0003), HLA-BC (49% vs. 27%, P=0.0053), B2m (38% vs. 21%, P=0.0048) and HLA-II (15% vs. 10%, P=0.0005) than low-grade conventional chondrosarcoma (grade 1). In addition the conventional chondrosarcoma (grade 1,2 and 3) express less HLA-A (31% vs. 83%, P<0.0001), HLA-BC (42% vs. 90%, P<0.0001), B2m (32% vs. 59%, P=0.0002) and HLA-II (67% vs. 14%, P<0.0001) antigens compared to dedifferentiated chondrosarcoma.

Grade 3 conventional chondrosarcoma have more $CD8^+$ lymphocytic infiltration compared to grade 1 and 2 chondrosarcoma combined: 3.4 ± 2.7 (range, 0-14, n=5) vs. 0.26 ± 0.21 (range, 0-7.6, n=37) lymphocytes per measured field, (P=0.014). Furthermore the conventional chondrosarcoma contain less $CD8^+$ infiltrate than dedifferentiated chondrosarcoma with a difference of 0.63 ± 2.5 (range, 0-14, n=42) versus 14 ± 15 (range, 0-52, n=20) lymphocytes per measured field, (P<0.0001).

Conclusions: In this study we show the frequent downregulation of HLA-expression in conventional chondrosarcoma and to a lesser degree in dedifferentiated chondrosarcoma. Further we revealed the higher HLA-expression and corresponding CD8 lymphocytic infiltration in the higher-grade conventional chondrosarcoma. The dedifferentiated chondrosarcoma have both a higher HLA expression as well as more CD8 lymphocytic infiltration compared to conventional chondrosarcoma. The HLA class I antigen – tumor antigen peptide complexes on the tumor cells' surface are needed for the immune system to have effective recognition by cognate T-cells and our data is therefore relevant when considering

chondrosarcoma for immunotherapy. High-grade chondrosarcoma seem to be good candidates for immunotherapy and dedifferentiated chondrosarcoma even better with high HLA expression and lymphocytic infiltration.

Figure 1. Lower HLA class I antigen expression in conventional than in dedifferentiated chondrosarcoma. Each bar indicates the mean percentage of stained tumor cells

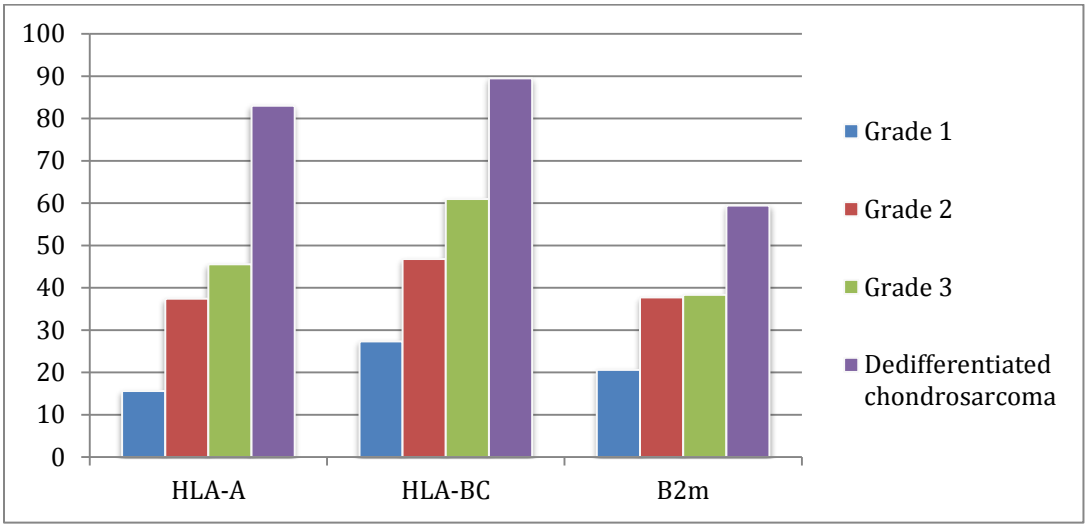

Figure 2. Lower CD8 lymphocytic infiltration in conventional than in dedifferentiated chondrosarcoma. Each bar indicates the actual average infiltrating CD8 lymphocytes per measured field.