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Abstract

Cutaneous angiosarcoma (CAS) is a highly malignant tumor with few effective treatments. Although the indication for immune checkpoint inhibitors such as anti-PD-1 antibodies is expected to expand, there are many unknowns regarding the tumor immune microenvironment in CAS, which is generally considered an immunologically "cold" tumor. Our previous study demonstrated that tertiary lymphoid structures (TLSs) were associated with a favorable prognosis in CAS. However, we still don't know what the difference is between cases of TLS-rich and TLS-poor. Furthermore, the number of TLSs can vary significantly between lesions in the same case, for example, between primary and recurrent lesions. To analyze the changes in the tumor immune microenvironment in CAS in more detail, we performed comprehensive RNA sequencing using a Next-generation sequencer (NGS). Sixty-two samples from 31 cases of CAS treated at Nagoya City University were collected. NGS and gene set enrichment analysis (GSEA) were performed on 15 samples among them. Immunohistochemistry and prognostic analysis by Kaplan-Meier method were performed on all 62 samples. NGS results showed that NY-ESO-1 (CTAG1B) was significantly upregulated in the TLS-positive cases. Immune checkpoint molecules including programmed death-1 (PD-1) and programmed death-ligand 1 (PD-L1) were upregulated in TLS-negative or TLS-low cases and seemed to associate with the suppression of TLS formation. In a comparison of primary and recurrent lesions, other cancer-testis antigens (CTAs) including XAGE-1B were significantly upregulated in recurrent lesions. The number of infiltrating CD8-positive cells and TLSs showed no significant trend between primary and recurrent lesions. However, the PD-L1 expression of tumor cells was significantly lower in recurrent than in primary lesions. Chemokines correlated with NY-ESO-1 expression were CCL21 and CXCL8, and only CCL21 correlated with the number of TLS. There was no chemokine associated with XAGE-1. NY-ESO-1 and XAGE-1 are detectable by immunohistochemistry. Although each cannot be a prognostic marker by itself, they can be a helpful marker in combination with the number of TLSs. CTAs play an essential role in forming the tumor immune microenvironment in CAS. These findings are evidence that CAS is an immunologically "hot" tumor and provides us with potential therapeutic targets and encourages the expansion of immunotherapy indications.