

Utility of Immunohistochemistry With Antibodies to SS18-SSX Chimeric Proteins and C-Terminus of SSX Protein for Synovial Sarcoma Differential Diagnosis

Lasota, Jerzy MD^{*}; Chłopek, Małgorzata PhD^{*†}; Kaczorowski, Maciej MD^{*‡}; Natálie, Klubíčková MD[§]; Ryś, Janusz MD^{||}; Kopczyński, Janusz MD[¶]; Sulaieva, Oksana MD[#]; Michal, Michael MD[§]; Kruczak, Anna PhD^{||}; Harazin-Lechowska, Agnieszka MD^{||}; Szczepaniak, Magdalena MSc[†]; Koshyk, Olena MD^{**}; Hałóń, Agnieszka MD[‡]; Czapiewski, Piotr MD^{††,‡‡}; Abdullaev, Zied PhD^{*}; Kowalik, Artur PhD^{†,§§}; Aldape, Kenneth D. MD^{*}; Michal, Michal MD[§]; Miettinen, Markku MD^{*}

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Abstract

Synovial sarcoma is a relatively common soft tissue tumor characterized by highly specific t(X;18)(p11;q11) translocation resulting in the fusion of SS18 with members of SSX gene family. Typically, detection of SS18 locus rearrangement by fluorescence in situ hybridization or SS18::SSX fusion transcripts confirms the diagnosis. More recently, immunohistochemistry (IHC) for SS18-SSX chimeric protein (E9X9V) and C-terminus of SSX (E5A2C) showed high specificity and sensitivity for synovial sarcoma. This study screened a cohort of >1000 soft tissue and melanocytic tumors using IHC and E9X9V and E5A2C antibodies. Three percent (6/212) of synovial sarcomas were either negative for SS18-SSX or had scattered positive tumor cells (n=1). In these cases, targeted RNA next-generation sequencing detected variants of SS18::SSX chimeric transcripts. DNA methylation profiles of 2 such tumors matched with synovial sarcoma. A few nonsynovial sarcoma tumors (n=6) revealed either focal SS18-SSX positivity (n=1) or scattered positive tumor cells. However, targeted RNA next-generation sequencing failed to detect SS18::SSX transcripts in these cases. The nature of this immunopositivity remains elusive and may require single cell sequencing studies. All synovial sarcomas showed positive SSX IHC. However, a mosaic staining pattern or focal loss of expression was noticed in a few cases. Strong and diffuse SSX immunoreactivity was also seen in epithelioid sclerosing osteosarcoma harboring *EWSR1::SSX1* fusion, while several sarcomas and melanocytic tumors including cellular blue nevus (5/7, 71%) revealed focal to diffuse, mostly weak to intermediate SSX staining. The SS18-SSX and SSX IHC is a useful tool for synovial sarcoma differential diagnosis, but unusual immunophenotype should trigger molecular genetic testing.