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[SAMPLE]

Use of *p16* fluorescence in situ hybridization (FISH) for differential diagnosis of mesothelioma in smear preparations

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[Objective]: Malignant pleural mesothelioma (MPM) is an aggressive tumor with a poor prognosis. Completion of trimodality treatment during early stages of the disease leads to longer patient survival, suggestive of importance of early diagnosis. **[Methods]:** The effusion cytology can be used to identify MPM cells in pleural effusions during early stages of the disease. However, morphological discrimination of MPM cells from reactive mesothelial hyperplasia (RMH) cells is difficult, especially during the early disease period. Application of *p16* fluorescence in situ hybridization (FISH) to histologic or cytologic specimens can be used to discriminate MPM from RMH cells because of the high specificity of the homozygous deletion of *p16* (CDKN2A), which is present in MPM but not in RMH cells. Correlations of *p16* status between cells in pleural effusions and underlying mesothelioma tissues in the pleura have not been described. **[Results]:** We used *p16* FISH to investigate 21 MPM cases that had smears prepared from pleural effusions and mesothelioma tissues obtained using biopsy or surgery. The *p16* homozygous deletion was present in 14/21 (66.7%) of the cases. Both the cytologic preparations and tissue sections were deletion positive in each of the 14 cases. For each of the seven cases without the *p16* deletion in mesothelioma tissue, the deletion was also not present in the smear preparation. Thus, *p16* deletion in cytologic preparations is strongly associated with *p16* deletion in underlying mesothelioma in the pleural tissue. These results indicated that detection of the *p16* homozygous deletion using FISH can be used as a marker of malignancy in cytologic preparations. As we previously reported, a combination of virtual microscopy and FISH is useful for this application. Cells on smear preparations are recorded using a virtual microscope system and subjected to FISH analysis, followed by identification and morphological analysis of *p16* homozygous deletion positive cells. **[Conclusion]:** When the deletion is positive, *p16* FISH works as a marker of malignancy. When deletion is negative, morphological characteristics that are revealed using an analysis of *p16* homozygous deletion positive mesothelioma cells serve as clues for an accurate diagnosis.