is addressed on page 71 of the WHO blue book, where it also stated that NE stains are not recommended for routine use in tumors lacking NE morphologic features. The WHO committee did not consider this problem important enough to warrant a formal title in the classification; however, the recommendation that testing for NE immunohistochemical markers in the absence of NE morphologic features not be performed in either the nonresection or resection specimen settings is important and should not be overlooked.

William D. Travis, MD
Department of Pathology
Memorial Sloan Kettering Cancer Center
New York, New York

Elisabeth Brambilla, MD
Department d’Anatomie et Cytologie Pathologiques
CHU Albert Michallon
University Joseph Fourier
INSERM U823 Institut Albert Bonniot
Grenoble, France

Andrew G. Nicholson, DM, FRCPath.
Department of Pathology
Royal Brompton Hospital
London, United Kingdom

References

Genetic Basis of Mesothelioma—More Than Asbestos Exposure

To the Editor:
A combination of pathogenic organisms, environmental carcinogen, and genetic predisposition can contribute to carcinogenesis. No causative viruses for mesothelioma have been identified to date, and even though mesothelioma has been attributed largely to asbestos exposure, the genetic basis underlying the disease has lately received attention. Such interest is warranted because asbestos alone cannot explain the varying incidence of mesothelioma among patients with comparable exposure, and most diseases have a multifactorial etiology.

Thus, researchers were excited to find that mutations in a tumor suppressor gene, breast cancer 1–associated protein 1 (BAP1), were found in families with a high incidence of mesothelioma, as well as in sporadic cases.1 Interestingly, both germline and somatic mutations were found, which indicated a possible inheritance of the disease, as well as establishment of BAPI as a target of mutations. All family members had nonoccupational, residential asbestos exposure; thus, the relationship between BAPI mutations and asbestos might be additive, synergistic, or both.

Recently, Nasu et al.2 found somatic mutations of BAPI in more than 60% of 22 frozen mesothelioma biopsies, and they duplicated their finding in another 70 biopsy samples. There was no significant correlation between frequency of BAPI mutations and asbestos exposure among patients, which implied that the pathogenesis of mesothelioma may be multifactorial and possibly polygenic.

For instance, germline and somatic mutations in transcriptional regulators such as mammalian switch/sucrose nonfermentable (mSWI/SNF) chromatin remodeling complex were noted in mesothelioma.3 Such mutations may cause low acetylation of histone and affect transcription, thereby contributing to the development of mesothelioma. Even though these results were obtained from eight mesothelioma cell lines from patients who all had a history of asbestos exposure, they supported interplay between genetic predisposition and asbestos as a contributor to development of disease.

Furthermore, somatic mutations were reported in tumor suppressor genes, including neurofibromatosis type 2 (NF2), large tumor suppressor 2 (LATS2),
cyclin-dependent kinase inhibitor 2A (CDKN2A), and Cullin 1 (CUL1), in mesothelioma cell lines and tissues.\textsuperscript{4,5} Many of these mutations affect pathways, including the Hippo, cell cycle, mitogen-activated protein kinase (MAPK), and wingless-type (Wnt) pathways. In addition to somatic mutations, several fusion transcripts, such as LAT51–presenilin 1 (PSEN1), were identified. A downstream effect of such fusion was the inability to suppress mesothelioma cell growth in vitro. The cell lines and tissues originated from patients, many of whom reported asbestos exposure (and some who did not might have had residential exposure).

Reports in the literature thus far point toward asbestos exposure as the predominant cause of mesothelioma, with susceptibility increased by genetic predisposition. Whether a genetic mutation by itself is sufficient to cause mesothelioma has not been shown, yet. With identification of new candidate genes and clarification of their function in the context of mesothelioma, our understanding of its carcinogenesis will increase even further.

**MET Gene Status in Malignant Mesothelioma Using Fluorescent In Situ Hybridization**

To the Editor:

In our October 2015 letter in the *Journal*\textsuperscript{1} we reported a patient with malignant mesothelioma (MM) with amplification of the MET gene associated with MET receptor expression. This finding suggests that the inhibition of MET might be used as a targeted therapy also in selected patients with MM.\textsuperscript{2}

We now report a MET copy number analysis in patients with MM scored by the Union for International Cancer Control criteria proposed for stratification of non–small cell lung cancer according to the EGFR fluorescence in situ hybridization (FISH) assay and also used by Go et al.\textsuperscript{3} for the scoring of MET. MET status was classified as FISH-positive and -negative according to the frequency of MM cells with specific copy numbers of the MET gene and chromosome 7 centromere (CEP7).\textsuperscript{3}

This study was approved by the Liguria Region Ethics Committee, and written informed consent was obtained from all patients.

We analyzed 60 patients with MM (male, 66.7%; median age, 60.0 years [range, 5–85 years]), including patients with epithelioid (n = 36), sarcomatoid (n = 12), biphasic (n = 8), desmoplastic (n = 2), and papillary (n = 2) subtypes. Thirty cases of MM were from a tissue microarray (MS801; US Biomax Inc, Rockville, MD), 12 cases of formalin-fixed paraffin-embedded tissues were from the Unit of Pathology, IRCCS A.O.U. San Martino–IST (Genova, Italy), and 18 cases were from the Division of Histopathology (ASL5, La Spezia, Italy).

We found 5 FISH-positive cases (8.3%), of which one epithelioid MM had MET amplification (about 8 MET signals on >70% of cells; MET/CEP7 ratio = 4.0; Fig. 1A) and four epithelioid MMs showed high polysomy of MET (range of 4–10 spots of MET in about 60%–80% of MM cells; a representative case is shown in Fig. 1D). All the other 55 FISH-negative cases (91.7%) were disomic for MET (a representative case is shown in Fig. 1G).

As in the previously reported case, IHC analysis showed that amplification was associated with moderate expression of MET protein in cytoplasm and membrane of MM cells (Fig. 1B). In contrast, high gene polysomy resulted in low staining of MET protein (Fig. 1E).

In our study, we found that MET amplification is a rare event in patients with MM (1.7% of total cases) in contrast to MET polysomy, which occurs more frequently (6.7% of total cases). The biological impact of MET polysomy on cancer cells has not been well established. However, highly polysomic status in MM