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VERDICT REPORT

Asbestos is *Not* the Only *Known* Cause of Mesothelioma

A Commentary by Edward R. Hugo of Hugo Parker LLP
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It is now ***known*** that additional causes of mesothelioma include exposure to other types of mineral fibers (such as erionite), radiation and naturally occurring mesothelioma arising in the setting of pathogenic germline mutations, also known as gene-related mesothelioma.[1] Cancers are caused by the accumulation of genetic mutations that may be inherited, induced by environmental factors, or as a result of DNA replication errors (*i.e.*, spontaneous cell division errors).[2] Like other cancers, "irrespective of exposure and of inherited mutations, some mesotheliomas may occur because of the inevitable accumulation of spontaneous mutations… ."[3]

The evidence supporting the existence of "gene-related malignant mesotheliomas" that are unrelated to asbestos exposure includes the following: (1) lack of temporal relation between mesothelioma in women and historic use of commercial forms of asbestos (*i.e.*, the age-adjusted mesothelioma incidence in U.S. women from 1973 to 2008 has been stable while the commercial use of asbestos has dramatically declined); (2) the occurrence of mesothelioma in children aged below the lowest recorded latent period for occupational asbestos-associated mesotheliomas; (3) cases of mesothelioma in persons with no history of asbestos exposure despite extensive investigation and/or with no detectable fibers in a fiber burden analysis; and (4) the spontaneous occurrence of various cancers, including mesothelioma, in animals.[4]

Plaintiffs' counsel argue that their clients with genetic germline variants (or "mutations") are "egg shell" plaintiffs, *i.e.*, that they are merely *more susceptible* to asbestos causing their mesothelioma than the average person. However, that is merely an argument because there is no evidence that a background level of exposure to asbestos can inactivate the suppressor genes that result in mesothelioma in humans. A recent animal study comparing the rate of spontaneous mesotheliomas in mice with and without germline genetic mutations in the absence of asbestos exposure refutes the "egg shell" plaintiff argument.[5] And, historical observations of mesothelioma developing in different animals demonstrates that the disease is naturally occurring:

> Mesotheliomas have been found sporadically in nonexperimental settings in at least eight different animal species, including *fish* (*bass*-Harshbarger, 1965-1973; *trout* - - Herman, 1985}: *wild rats* (Norvegicus-McCoy, 1909; Woolley and Wherry, 1911}; *hamsters* (Arnold *et al*., 1976: Mehnert *et al*., 1974; Fortner, 1961); *mastomys* (Solleveld, 1978; Solleveld *et al* ., 1984); *domestic* (Ilgren *et al.*, 1982) and *wild dogs* (Stewart, 1964); *leopards* (Ilgren *et al*., 1982); *elands* (Ilgren *et al.*, 1982); and *adult* (Baskerville, 1967) Purmann, 1930; Misdorp, 1963; Grant, 1958; Smith and Jones, 1957). *neonatal* (Grant, 1958), and *fetal* (Henschen and Alegrin, 1927; Drieux *et al*., 1949) *cows*.[6]

Cancer predisposition syndromes are caused by inherited pathogenic mutations in tumor suppressor genes.[7] BRCA1 Associated Protein-1 ("BAP1") is located on chromosome 3 and acts as a tumor suppressor, meaning that it helps prevent cells from growing uncontrollably and turning into cancer. The BAP1 tumor suppressor gene regulates tumorigenesis at two stages: initiation and progression. At the first stage, loss or inactivating mutations of BAP1 impairs its ability to repair DNA damage and to induce apoptosis (natural programmed cell death) resulting in accumulation of genetic mutations, genomic instability and the initiation of cancer. At the second stage, loss of BAP1 function allows the cancer cells to revive their metabolism to promote growth, survival and proliferation, including tumor metastasis.[8 9] Thus, BAP1 tumor predisposition syndrome ("TPDS") causes "gene-related malignant mesothelioma" in the absence of asbestos exposure and is a distinct etiology from asbestos-related malignant mesothelioma.[10 11 12 13 14 15 16]

Checkpoint Kinase 2 ("CHEK2") is a tumor suppressor gene that encodes the protein CHK2. It is located on chromosome 22 and like BAP1 is involved in DNA repair, cell cycle arrest and apoptosis in response to DNA damage. Mesothelial cells are continually subjected to endogenous sources of DNA damage, even without exposure to asbestos,

including replication stress, reactive oxygen species generated by cellular metabolism and transcription-replication conflicts.[17] Normally, CHK2 senses such insults and either prevents proliferation to permit cell repair or terminates damaged cells by apoptosis.[18 19 20] But, cells expressing CHEK2 result in attenuated checkpoint activation, incomplete cell cycle arrest and reduced apoptosis after genotoxic stress.[21 22 23 24] Thus, like a mutant BAP1 gene a mutant CHEK2 gene can drive mesothelioma in the absence of asbestos exposure.

The differences between gene-related malignant mesothelioma ("GR-MM") and asbestos-related malignant mesothelioma ("AR-MM") include the following:

Asbestos Exposure:
GR-MM: develops in the absence of exposure above ambient levels.

AR-MM: develops in response to exposure above ambient levels.

Latency:
GR-MM: occurs in children aged below the lowest recorded latency period for AR-MM.

AR-MM: occurs after a generally accepted minimum latency of 10 years.

Age at Diagnosis:
GR-MM: Median age is approximately 55.

AR-MM: Median age is approximately 72.

Gender Susceptibility:
GR-MM: Male to female ratio of 1:1.

AR-MM: Male to female ratio of 5:1.

"...Coupled with advances in genomics, it is now known that pathogenic germline mutations, in the absence of asbestos exposure, cause malignant mesothelioma."

Site Distribution:
GR-MM: Pleural to peritoneal ratio of 1:1.

AR-MM: Pleural to peritoneal ratio of 10:1.

Initial Clinical Symptoms:
GR-MM: Minimal to asymptomatic.

AR-MM: Serious and progressive.

Histology/Morphology:
GR-MM: Usually low grade epitheliod subtype with rare mitosis, minimal necrosis and early superficial invasion.

AR-MM: Histology includes epitheliod, sarcomatoid and biphasic subtypes with aggressive features and higher mitosis and necrosis.

Survival:
GR-MM: Median survival of 6 years with some patients surviving over 20 years.

AR-MM: Median survival of 16 months with virtually no long-term survivors.

Conclusion

The differences in asbestos exposure, latency, age at diagnosis, gender susceptibility, site distribution, clinical symptoms, histology/morphology and survival demonstrate that GR-MM and AR-MM are different diseases with different causes. Coupled with advances in genomics, it is now ***known*** that pathogenic germline mutations, *in the absence of asbestos exposure*, cause malignant mesothelioma.

Footnotes

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