

Therapeutic Radiation-Induced Malignant Mesothelioma after Primary Malignancy in Childhood

ISSN: 2690-9707



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Submission:  August 02, 2024

Published:  October 08, 2024

Volume 3 - Issue 4

How to cite this article: Denis R Miller¹, Bin Cho, Hyeon Jin Park and Jun Ah Lee. Therapeutic Radiation-Induced Malignant Mesothelioma after Primary Malignancy in Childhood. *Associative J Health Sci.* 3(4). AJHS. 000566. 2024.
DOI: [10.31031/AJHS.2024.03.000566](https://doi.org/10.31031/AJHS.2024.03.000566)

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Abstract

Background: This report provides clinical-pathological and epidemiologic data on four cases of malignant mesothelioma following prior multimodality therapy, including therapeutic radiation given for a primary childhood malignancy, including neuroblastoma, malignant mesothelioma, embryonal rhabdomyosarcoma (ERMS), and acute myelomonocytic leukemia (AMML).

Material and Methods: The medical records from the three US patients were reviewed by the senior author who provided medical testimony for litigation, now resolved. Medical records were reviewed and summarized by the attending physicians in the Republic of Korea.

Result: The diagnoses of the initial cancers and secondary mesothelioma were confirmed by standard medical imaging, and histologic and immunohistochemical methods. The latencies were 51 years, 34 years, 36 years, and 17 years respectively after neuroblastoma, childhood metastatic mesothelioma, embryonal rhabdomyosarcoma, and acute myelomonocytic leukemia (AMML). Cases 1, 2, and 3 were treated with debulking surgery and standard chemoradiotherapy and survived for 12, 13, and 13 months respectively. All three were exposed para-occupationally and/or in their households to asbestos. Case 4 received multiagent chemotherapy, whole body radiation, and allogeneic bone marrow transplant for AMML and standard chemotherapy and surgery for mesothelioma but was never exposed to asbestos.

Conclusion: The relevant epidemiology data on radiation-induced mesothelioma and the lesser contributory role of household or environmental/occupational exposure to asbestos in Cases 1, 2, and 3 suggest that therapeutic radiation was the primary cause of the secondary malignant mesothelioma in these three cases. Any additive or synergistic effect of asbestos exposure to therapeutic radiation is uncertain. The etiology of secondary malignant mesothelioma associated with therapeutic radiation remains a fertile field of investigation.

Keywords: Malignant mesothelioma; Therapeutic radiation; Chrysotile exposure; Second malignant neoplasm after primary neoplasm in childhood

Introduction

Whereas mesothelioma is the signal cancer caused primarily by occupational exposure to asbestos, not all cases are asbestos-related. Malignant mesothelioma unrelated to asbestos exposure occurs in up to 30% of cases [1]. Non-asbestos related associations have been observed after exposure to erionite mineral fibers, thorium dioxide, in atomic energy workers, and following chronic serosal inflammation, therapeutic radiation, and germline or somatic gene mutations [2]. The focus of this report is therapeutic radiation [3,4]. which has been implicated in case reports and more compellingly in epidemiologic studies.

Material and Methods

The medical records of cases 1, 2, and 3 were made available to the author (DRM) while serving as a medical expert for defendants in asbestos litigation, now resolved. Case 4, from the Republic of Korea occurred a child not involved in litigation and was never exposed to asbestos. Because of the long interval between the diagnosis of neuroblastoma and mesothelioma in the first case, complete records on radiation therapy administered were unavailable. The patient was treated at an academic center and in the absence of these details, the published standard of care at the time was used as a surrogate [5]. Based on other adverse effects of radiation therapy noted in source document entries, it is reasonable to conclude that the patient received therapeutic radiation to the abdominal cavity. Details of the second patient's initial diagnosis and treatment of metastatic mesothelioma were available in a report published in 1991 [6].

Case Reports

Case 1

Stage 3 neuroblastoma of the left adrenal was diagnosed at age 5 years and treated with partial resection and partial pancreatectomy. He was treated with chemotherapy and abdominal radiation therapy. Splenic vein thrombosis at age 11 prompted a splenectomy. He developed insulin-dependent diabetes mellitus at 22 and bilateral renal atrophy at age 36 necessitating a kidney transplant at age 42. At age 50, arteritis of abdominal vessels necessitated bowel resection and mesenteric angioplasty. At 56 years of age, he developed widespread peritoneal and pleural masses and diagnosed as metastatic mesothelioma. Chemoradiation were unsuccessful and he died 13 months after diagnosis. He was exposed to asbestos cement pipes one summer and to automotive friction parts, and household roofing and insulation materials.

Case 2

At 9 years of age, the patient developed Crohn disease. Medical imaging revealed a right pleural effusion, abdominal/pelvic masses, and ascites with negative cytology. Biopsies indicated diffuse, well-differentiated, epithelioid malignant mesothelioma with metastases to the left neck and thorax and was treated with chemotherapy and 1900cGy radiation to the left lung apex. At 44 years of age, left pleural thickening and increased uptake on PET scan in the prior radiation field led to the diagnosis of secondary, not recurrent epithelioid mesothelioma. She died 13 months later. Her asbestos exposures were to her trucker father's and later her husband's work clothes, the latter which she laundered.

Case 3

At 7 years the patient was diagnosed with stage IIB embryonal rhabdomyosarcoma (ERMS) of the left posterior occipital area and cervical/supraclavicular area. He was treated with chemotherapy and localized involved field radiation (~4500-5800cGy). He developed shortened LVEF, alopecia, left neck atrophy, and hypothyroidism, all related to radiation therapy. Fifteen years later,

after sustaining a life-threatening motorcycle accident requiring thoracotomy, resection of a left apical mass revealed malignant pleural mesothelioma. He was treated with chemotherapy with a temporary complete response only to have a recurrence five months later and treated with nivolumab and ipilimumab immunotherapy. His disease progressed and he succumbed 14 months after the diagnosis. His alleged exposure to asbestos was from baby powder used by his parents and grandparents personally and on him. He observed his father repairing automotive friction parts on 2-3 family cars. His family history was positive for lung cancer, skin cancer, and melanoma.

Case 4

Case 4 was diagnosed with AMML at 5 years of age. Standard induction therapy resulted in complete remission. After consolidation chemotherapy and a conditioning regimen that included whole body irradiation, he underwent allogeneic bone marrow transplantation. At 22 years of age, he developed progressively worsening chest discomfort, dysphagia, dyspnea on exertion, and weight loss. Imaging revealed an 8x5.2cm mass in the right middle lobe, pleura and diaphragm without pleural effusion. Histopathology revealed sarcomatoid malignant mesothelioma with confirmatory immunohistochemistry (IHC). Chemotherapy and radiation therapy were unsuccessful, and his disease progressed. He and his family elected to discontinue therapy. Presumably he died but as he was lost to follow-up, no further information is available. He was not exposed to any known source of asbestosis.

Discussion

Malignant mesothelioma is an extremely rare malignancy in adults and even rarer in children. Approximately 3,000 new cases of mesothelioma are diagnosed annually in the United States, virtually all in adults [7]. The total number of cases reported in children is under 200, but the exact incidence remains unknown [8,9]. This report will review the role of therapeutic radiation-induced mesothelioma after successful treatment of four different primary malignancies in childhood. Of the four, occurrence in three of the primary malignancies (neuroblastoma, malignant mesothelioma, and ERMS) have not been reported previously. Any potential contribution of asbestos exposure will also be discussed.

Although many other cases of radiation-induced mesothelioma, primarily in patients with lymphomas, have been published, cases 1, 2, and 3 are unique. Case 1 is the first report of malignant peritoneal mesothelioma after radiation therapy for childhood neuroblastoma. Case 2 is the first report of malignant pleural mesothelioma as a second malignant neoplasm (SMN) after radiation therapy for metastatic primary malignant mesothelioma in a child, rare as that is. Case 3 is the first reported case of radiation-induced mesothelioma after childhood ERMS. Certain atypical aspects of the three cases, the long latency in all 4 cases, the possible contribution of non-occupational asbestos exposure in cases 1, 2 and 3; and the question of profoundly delayed recurrence of a primary tumor (mesothelioma) versus a true SMN of the same type) warrant discussion.

Review of literature on mesothelioma after therapeutic radiation in childhood and adolescence

Therapeutic radiation is an established carcinogen. In addition to killing tumor cells, radiation therapy can directly damage normal tissue in the radiation field resulting in organ dysfunction and rarely SMN.

Single or multiple case reports alone are useful for hypothesis-testing but do not prove cause and effect. Large, well-designed epidemiology studies provide a higher degree of evidence and are more credible. Many have been identified in the Surveillance, Epidemiology, and End Results (SEER) database [10,11]. Of note is that SEER data do not record the source, dose, or fields of radiation therapy, occupational and non-occupational history, exposures to asbestos or other carcinogens, or family history. Teta et al. [10] identified patients with Hodgkin lymphoma (HL) and non-HL who developed a secondary malignant mesothelioma. The incidence of malignant mesothelioma was significantly increased in irradiated patients but not in the non-irradiated group. The authors concluded that radiotherapy is a cause of mesothelioma. A recent update confirmed these findings and minimized any contribution of exposure to asbestos [11].

In a report from Netherlands, among 2,567 5-year survivors of HL [12], the risk of developing mesothelioma was 26-fold higher in irradiated HL patients compared to the general population. Other large epidemiological studies of radiation-associated second malignant neoplasms in NHL and HL have been reported [13,14].

Additional data, albeit weaker, on the etiologic role of therapeutic radiation come from single or multiple case reports of pediatric patients who received radiation therapy for Wilms tumor [15] and after hematopoietic stem cell transplantation [16].

The dose range of therapeutic radiation given to children and capable of causing a SMN is broad and depends on many factors including the primary malignancy and its extent and location, the patient's age, and whether surgery and/or chemotherapy are given. The administered radiation therapy has major adverse effects on local organs and tissues including the pancreas, kidneys, small and large intestines and their vasculature. The doses given to all four children have been associated with therapeutic radiation induced malignant mesothelioma.

Specifically relevant to Case 1, an extensive search of the English-language literature since 1981 keying on peritoneal mesothelioma after abdominal radiation for a primary pediatric cancer uncovered 30 additional cases, but no cases of malignant peritoneal mesothelioma [17]. The poor prognosis of advanced stage pediatric malignancies would contribute to the observed low incidence of radiation-induced mesothelioma in these patients. Other factors contributing to the risk of developing radiation-induced mesothelioma include acquired or inherited genetic mutations [2] age, and immunodeficiency.

In addition to the rarity of malignant mesothelioma in the pediatric population, virtually every publication agrees that unlike

in adults, there is no clear causal association between childhood mesothelioma and asbestos exposure or irradiation. Confidence in this statement requires a detailed and complete history of any possible environmental or bystander exposures in the affected child. Recent reports attributing malignant mesothelioma in adulthood to exposure to asbestos or asbestiform-fiber contaminated talcum powder have not established a clear-cut relationship but have generated considerable litigation [18,19].

Mesothelioma in automotive mechanics and their household bystanders

Chrysotile is largely the only form of asbestos that was used in automotive friction parts, home improvement, and cement pipe materials in the United States until the 1980s and comprised about 30%-80% of the finished product. Chrysotile has been banned since then, but compliance has not been 100%. The concentration of respirable chrysotile fibers liberated during brake repairs is low [20,21]. Most chrysotile fibers remain imbedded in the binding material. Compared to other longer straight amphibole fibers, chrysotile fibers have a curly shape, are short ($<5\mu$), are not retained in the lungs, and have less fibrogenicity, pathogenicity, and carcinogenicity than amphiboles. As a cautionary note, mechanics who developed mesothelioma may have had undocumented exposures to amphiboles. Roelofs et al. [22] reported the one outlier in Massachusetts automobile mechanics). Their data suggested an increased risk of mesothelioma, but 60% of the exposure details were missing and confounding occupational exposure including exposure to amphiboles cast doubt on the study's reliability. Finley et al. [23] analyzed cumulative lifetime exposure to chrysotile asbestos by brake mechanics during the period 1950-2000 (40). Cumulative lifetime exposures in auto mechanics were usually 100- to 1000-fold lower than those of other occupational groups with asbestos exposure for similar time periods.

Household or bystander exposure

Does household exposure to work clothes increase the risk of mesothelioma? Well-designed studies that simulated workplace and household environments and quantified asbestos exposure in relatives who laundered spousal work clothes or in bystanders (e.g., children) indicated that such exposures were within acceptable ambient levels and are not associated with mesothelioma-causing levels of asbestos [24-26].

Pierce et al. [27] reviewed data from 14 published studies and established a no observed adverse effect level (NOAEL) from exposure to chrysotile or crocidolite asbestos in occupational and non-occupational activities. The range of "best estimate" NOAELs was 208-415 f/cc-years in friction product manufacturing workers, cement workers, and textile workers, levels much higher than those levels related to the typical household domestic exposures.

It is logical that if a worker is exposed to low background levels of asbestos, their children's exposure is unlikely to be greater. Workers whose occupation involve low-level chrysotile exposure over a very short latency period are not at an increased risk of developing mesothelioma. It follows that co-habitants of these

workers would not have an increased risk of mesothelioma. The existing epidemiologic studies of domestically exposed populations support this hypothesis and clearly demonstrate that the risk for the domestically exposed individual is remarkably less than that of the worker.

Undoubtedly, asbestos exposure under certain conditions causes malignant mesothelioma. But for scientific plausibility, “asbestos exposure” requires some quantitative assessment as does the amount and type, duration, and concentration of asbestos exposure. To support this position, the “linear no threshold” (LNT) theory is cited. This theory claims that any exposure to asbestos above background is sufficient to cause malignant mesothelioma. More recent scientific evidence has discredited the theory and is derived from the papers published in 2019 in *Chemico-Biologic Interaction* (vol 301, pages 2-67) [28].

Mutations of genes associated with mesothelioma (e.g., BAP1) were not tested in any of these cases. Contentious is whether patients with a BAP1 or other mutations are more susceptible to low levels of asbestos exposure, not known to be carcinogenic. Carbone et al [2] suggest that a BAP1 mutation is sufficient to cause malignant mesothelioma, especially in the hereditary familial cancer syndrome. Xu et al. [29] have presented animal data suggesting that there may be additive or synergistic effects of BAP1 deletion or mutation. However, solid, confirmatory clinical and epidemiologic data supporting any such effect in a patient treated with therapeutic radiation are unavailable.

The hypothesis that exposure to baby other talcum powders contaminated with minute concentrations of asbestos and asbestiform fibers can cause ovarian cancer and malignant mesothelioma has not been confirmed by any well-designed, controlled clinical trials.

Summary and Conclusion

Four cases of malignant mesothelioma in adulthood after radiation therapy for a primary malignancy in childhood are presented: the first after adrenal neuroblastoma in a 5-year old, the second after metastatic peritoneal mesothelioma in a 10 year old followed by pleural mesothelioma 34 years later; third in an eight year who developed left cervical ERMS followed 37 years later with left apical pleural mesothelioma, and the fourth after allogeneic hematopoietic stem cell transplantation for AMML in an 8 year old Korean child. Therapeutic radiation is now recognized by the American Cancer Society and other organizations as a rare cause of malignant mesothelioma. Exposure to asbestos from many direct or indirect sources occurred in three of the four cases. However, mere exposure to asbestos does not prove carcinogenicity. Epidemiology studies in automotive mechanics and other non-high-risk occupations and paraoccupational exposures in relatives of workplace-exposed individuals indicate that the risk of mesothelioma is not increased. Simulated conditions showed that these levels are within non-carcinogenic NOAELs and would not have caused malignant mesothelioma. A large body of evidence has discredited the LNT theory. There are no controlled clinical trials attributing exposure to baby and cosmetic powders to malignant

pleural mesothelioma. Finally, currently data are not available showing an additive or synergistic effect of therapeutic radiation and low-dose asbestos exposures in causing mesothelioma.

Acknowledgement

Thanks to Albert Parnell, Erik Hawkins, Kevin Greene, and Andrew Scholz for providing the available medical records of cases 1, 2, and 3 for review. Mark Zellner offered stimulating discussion and references on the LNT theory. None were involved in the preparation or submission of the manuscript for peer-review.

Disclosure

No funding was obtained for the preparation of this manuscript. Case 2 was subject of a previous publication (Geary et al, *Am J Clin Path* 1991; 95: 493-99). Updated information on the case has not been published before. All the reported patients have died. Case 1 was the subject of a Daubert Hearing and jury trial in 2016. One of the authors (DRM) has performed consulting work for companies involved in asbestos litigation, but this work has not influenced the opinions presented in this paper.

References

1. Jasani B, Gibbs A (2012) Mesothelioma not associated with asbestos exposure. *Arch Pathol Lab Med* 136(3): 262-267.
2. Carbone M, Yang H, Pass HI, Krausz T, Testa JR, et al. (2013) BAP1 and cancer. *Nat Rev Cancer* 13(3): 153-159.
3. Goodman JE, Nascarella MA, Valberg PA (2009) Ionizing radiation: A risk factor for mesothelioma. *Cancer Causes Control* 20(8): 1237-12354.
4. Chiriac LR, Barletta JA, Yeap BY, et al. (2013) Clinicopathologic characteristics of malignant mesothelioma arising in patients with a history of radiation for Hodgkin and non-Hodgkin lymphoma. *J Clin Oncol* 31(36): 4544-4549.
5. Sutow WW, Vietti TJ, Fernbach DJ (1977) *Clinical Pediatric Oncology*. (2nd edn), TJ, CV Mosby Co, St. Louis, USA.
6. Geary WA, Mills SE, Pierson HF, Pope TL (1991) Malignant peritoneal mesothelioma in childhood with long-term survival. *Am J Clin Pathol* 95(4): 493-498.
7. Moolgavkar SH, Meza D, Turim J (2009) Pleural and peritoneal mesothelioma in SEER: Age effects and temporal trends 1973-2005. *Cancer Causes Control* 20(6): 935-944.
8. Thomas A, Chen Y, Yu T, Gill A, Prasad V, et al. (2015) Distinctive clinical characteristics of malignant mesothelioma in young patients. *Oncotarget* 6(18): 16766-16773.
9. Kelsey A (1994) Mesothelioma in childhood. *Pediatr Hematol Oncol* 11: 461-462.
10. Teta MJ, Lau E, Scurman BK, Wagner ME (2007) Therapeutic radiation for lymphoma: Risk of malignant mesothelioma. *Cancer* 109(7): 1432-1438.
11. Chang ET, Lau EC, Mowat FS, Teta MJ (2017) Therapeutic radiation for lymphoma and risk of second primary malignant mesothelioma. *Cancer Causes Control* 28(9): 971-979.
12. DeBruin ML, Burgers JA, Baas P, van't Veer MB, Noordijk EM, et al. (2009) Malignant mesothelioma following radiation treatment for Hodgkin's lymphoma. *Blood* 113(16): 3679-3681.
13. Schaapveld M, Aleman BMP, van Eggermond AW, Janus CPM, Krol ADG, et al. (2015) Second cancer risk up to 40 years after treatment for Hodgkin's lymphoma. *New Engl J Med* 373(26): 2499-2511.

14. Hodgson DC, Gilbert ES, Dores GM, Schonfeld SJ, Lynch CF, et al. (2007) Long-term solid cancer risk among 5-year survivors of Hodgkin's disease. *J Clin Oncol* 25(12): 1489-1497.
15. Antman KH, Ruxer RL, Jr, Aisner J, Vawter G (1984) Mesothelioma following Wilms tumor in childhood. *Cancer* 54(2): 367-369.
16. Miniero R, Tardivo I, DeSimone L, Gubetta L, Orecchia S, et al. (2003) Abdominal malignant mesothelioma following autologous bone marrow transplantation: a case report. *Ped Hematol Oncol* 20(8): 583-588.
17. Coffin CM, Dehner LP (1992) Mesothelial and related neoplasms in children and adolescents: a clinicopathological and immunohistochemical analysis. *Pediatr Pathol* 12(3): 333-347.
18. Applebaum MA, Henderson TO, Lee SM, Pinto N, Volchenboum SL, et al. (2015) Second malignancies in patients with neuroblastoma: the effects of risk-based therapy. *Pediatr Blood Cancer* 62(1): 128-133.
19. Ju HY, Moon EK, Lim J, Park BK, Shin HY, et al. (2018) Second malignant neoplasms after childhood cancer: A nationwide population-based study in Korea. *PLoS One* 13(11): e0207243.
20. Garabrant DH, Alexander DD, Miller PE, Fryzek JP, Boffetta P, et al (2016) Mesothelioma among motor vehicle mechanics: an updated review and meta-analysis. *Ann Occup Hyg* 60(1): 8-26.
21. Rake C, Gilham C, Hatch J, Darnton A, Hodgson J, et al. (2009) Occupational, domestic, and environmental mesothelioma risks in the British population: A case-control study. *Br J Cancer* 100(7): 1175-1183.
22. Roelofs CR, Kernan GJ, Davis LK, Clapp RW, Hunt PR (2013) Mesothelioma and employment in Massachusetts: Analysis of cancer registry data 1988-2003. *Am J Ind Med* 56(9): 985-992.
23. Finley BL, Richter RO, Mowat FS, Mlynarek S, Paustenbach DJ, et al. (2007) Cumulative asbestos exposure for US automobile mechanics involved in brake repair (circa 1950s-2000). *J Expo Sci Environ Epidemiol* 17(7): 644-655.
24. Goswami E, Craven V, Dahlgren DL, Alexander D, Mowat F (2013) Domestic asbestos exposure: a review of epidemiologic and exposure data. *Int J Environ Res Public Health* 10(11): 5629-5670.
25. Sahmel J, Barlow CA, Gaffney S, Avens HJ, Madl AK, et al. (2016) Airborne asbestos take-home exposure during handling of chrysotile-contaminated clothing following simulated full shift workplace exposures. *J Expo Sci Environ Epidemiol* 26(1): 48-62.
26. Adelmann A, Maskrey JR, Lotter JT, Chapman AM, Nembhard MD, et al. (2018) Evaluation of take-home exposure to asbestos-contaminated worker clothing following the abrasive sawing of cement pipe. *Inhal Toxicol* 29(12-14): 555-566.
27. Pierce J, Ruestow PS, Finley BL (2016) An updated evaluation of reported no-observed adverse effect levels for chrysotile asbestos for lung cancer and mesothelioma. *Crit Rev Toxicol* 46(7): 561-586.
28. Calabrese EJ (2019) The linear no-threshold (LNT) dose response model: A comprehensive assessment of the historical and scientific foundations. *Chemico-Biologic Interactions* 301: 6-25.
29. Xu J, Kadariya Y, Cheung M, Pei J, Talarchek J, et al. (2014) Germline mutation of Bap1 accelerates development of asbestos-induced mesothelioma. *Cancer Res* 74(16): 4388-4397.