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【 EDITORIAL 】

Malignant Pleural Mesothelioma in Patients Who Previously Received Radiotherapy for Their First Malignant Tumor

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In this issue, Nakashima, et al. reported the first Japanese case of malignant pleural mesothelioma (MPM) that developed 25 years after thoracic radiotherapy for Hodgkin's lymphoma without a history of asbestos exposure (1). A table of 29 similar cases in the literature (Table 1) (1-19) shows distinguishing features, which are summarized as follows: 1) women accounted for 55% of cases, which is much higher than the proportion of women who develop asbestos-related MPM (<20%); 2) the median age at the diagnosis of MPM was 44 years old, whereas asbestos-related MPM is usually diagnosed in the late 50s or older (20); 3) 66% of patients had received radiotherapy for their first malignant tumor before 30 years old; and 4) the median period of latency was 16 years, which was shorter than the median period from the initial asbestos exposure to death of MPM (estimated to be ≥32 years) (21, 22). These unique characteristics, which differ from the clinical profile of conventional asbestos-related MPM, underscore the association between radiotherapy and MPM.

However, the causal relationship between radiotherapy and MPM, the main focus of the current case, has been difficult to establish in humans, although a mouse model successfully showed that radiation exposure induced the development of malignant mesothelioma in the early 1970s (23). Bradford Hill proposed criteria to consider for connecting the association and causation, as follows: 1) strength of the association between a cause and a disease, 2) consistency in different circumstances, 3) specificity in the cause, 4) temporality of the cause that precedes the disease, 5) dose-response relationship between risk factors and the disease variables, 6) biological plausibility, 7) coherence with generally known facts concerning the natural history and biology of the disease, 8) experimental evidence, and 9) analogy with commonly accepted phenomena (24). The association between radiotherapy and MPM satisfies some of these criteria obviously, while further discussions are needed for others (Table 2).

The strength of the association can be measured by the size of the effect, such as hazard ratio (HR) and relative risk (RR) in epidemiological studies. A longitudinal analysis of the US Surveillance, Epidemiology, and End Results (SEER) database showed that external beam radiotherapy actually increased the risk of MPM, but its HR (95% confidence interval) was only 1.34 (1.01-1.77). This value is similarly high to the RR of 1.27 for the association between passive smoking and lung cancer in never smokers (25) but lower than the RRs of 4-6 for other subsequent malignant tumors in childhood cancer survivors (26). Furthermore, this study has an absolute limitation, as the authors did not directly obtain the history of asbestos exposure but instead derived a proxy measure of the exposure by modeling the RR of primary mesothelioma among men in the county of residence (27). The specificity is not met strictly, as it is always difficult to exclude completely non-occupational asbestos exposure, such as that from the neighborhood, domestic, and household (28). In addition, many of these patients received cytotoxic chemotherapy as well, which is generally considered to have carcinogenic effects. The dose-response relationship could not be demonstrated in the SEER study of radiation-induced MPM (27), nor was any association or tendency observed between the dose of radiotherapy and latent period in this case series summary (Table 1).

The current case reminds us strongly of the unmet need concerning effective strategies for the prevention and early detection of subsequent MPM as well as other malignancies in cancer survivors who received radiotherapy for their primary tumor.

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Table 1. Malignant Pleural Mesothelioma in Patients with a History of Radiothearpy but No Asbestos Exposure.

N	Type of the first tumor	RT dose (Gy)	Sex	Age at radio-therapy	Age at diagnosis	Latent period (years)	Histology	Survival time (outcome)	Reference
1	Hodgkin's lymphoma	Unknown	M	29	34	5	Sarcomatous	Unknown	(2)
2	Hodgkin's lymphoma	Unknown	M	27	34	7	Sarcomatous	9 months (death)	(3)
3	Breast cancer	46	F	30	40	10	Epithelial	4 years (alive)	(4)
4	Seminoma	30	M	33	57	24	Epithelial	2 months (death)	(5)
5	Wilms' tumor	Unknown	M	3	44	41	Epithelial	Unknown	(6)
6	Wilms' tumor	34	M	6	22	16	Unknown	42 months (death)	(6)
7	Wilms' tumor	15	M	2	16	14	Epithelial	Unknown	(7)
8	Breast cancer	45	F	34	64	30	Unknown	13 months (death)	(8)
9	Hodgkin's lymphoma	36	F	4	24	20	Epithelial	2 years (alive)	(9)
10	Hodgkin's lymphoma	40	F	13	22	9	Epithelial	5 months (death)	(10)
11	Breast cancer	50	F	65	75	10	Epithelial	Unknown	(11)
12	Breast cancer	45	F	37	72	35	Epithelial	Unknown	(11)
13	Hodgkin's lymphoma	Unknown	M	28	49	21	Epithelial	Autopsy diagnosis	(12)
14	Hodgkin's lymphoma	40	F	21	43	22	Mixed	Autopsy diagnosis	(12)
15	Hodgkin's lymphoma	42	M	20	31	11	Epithelial	4 months (death)	(12)
16	Breast cancer	Unknown	F	49	78	29	Epithelial	Unknown	(12)
17	Hodgkin's lymphoma	35	M	32	46	14	Unknown	12 months (death)	(13)
18	Hodgkin's lymphoma	35	M	7	32	25	Unknown	Unknown	(13)
19	Hodgkin's lymphoma	38	M	7	18	11	Epithelial	7 months (alive)	(14)
20	Ovarian Sertoli Leydig cell tumor	36.5	F	11	20	9	Epithelial	9 years (alive)	(14)
21	Hodgkin's lymphoma	36	M	40	64	24	Unknown	6 years (alive)	(15)
22	Hodgkin's lymphoma	Unknown	F	18	30	12	Epithelial	Unknown	(16)
23	Lung cancer	60	F	49	66	17	Epithelial	5 months (death)	(17)
24	Breast cancer	Unknown	F	50	60	10	Epithelial	Unknown	(18)
25	Non-Hodgkin's lymphoma	Unknown	F	29	45	16	Epithelial	2 years (death)	(19)
26	Follicular lymphoma	Unknown	M	26	68	42	Sarcomatoid	14 months (death)	(19)
27	Hodgkin's lymphoma	Unknown	F	22	31	9	Epithelial	7 months (death)	(19)
28	Hodgkin's lymphoma	Unknown	F	22	54	32	Epithelial	10 months (death)	(19)
29	Hodgkin's lymphoma	50	F	25	50	25	Epithelial	Alive	(1)

Table 2. Hill's Criteria of Causation and Their Application to the Case of Radiotherapy and MPM.

Hill's criteria of causation	Discussion	Meet the criteria
1. Strength	An epidemiological study showed that radiotherapy increased a risk of MPM, but its hazard ratio was only 1.34.	Controversial
2. Consistency	The similar association between radiotherapy and MPM is also observed in other patients (Table 1).	Yes
3. Specificity	There are several other causal factors of MPM including asbestos.	No
4. Temporality	MPM develops years after radiotherapy.	Yes
5. Dose-response relationship	No dose-response was obserbed between the radiation dose and MPM development.	No
6. Biological plausibility	Radiation is an established carcinogen.	Yes
7. Coherence	MPM develops years after carcinogen exposure.	Yes
8. Experimental evidence	An experiment showed that radiation exposure developed malignant mesothelioma in mice.	Yes
9. Analogy	Association between radiotherapy and malignant tumors are frequently observed.	Yes

MPM: malignant pleural mesothelioma

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