Histopathological Studies on Radiation Pneumonitis

By
Tsuneo Namiki

From the Department of Pathology, Tohoku University School of Medicine; Director: Prof. K. Akazaki

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INTRODUCTION

Studies on radiation pneumonitis have been made from the beginning of the 20th century in Europe and America. Prior to the Second World War, many articles have appeared including the works of Engelstad and Warren et al. who described the general aspects of this problem. In Japan, the incidence of this disease has been rare. A case report by Hamaguchi and Akazaki was only available before the Second World War. Recently, with a remarkable improvement of the method of radiation, a large dosage of radiation is administered over a long period of time. Consequently, this disease has frequently been observed, and many reports have come out since around 1955. However, histopathological study on this disease is few. The pattern of disease and the mechanism of its occurrence are still obscure in many ways.

Considering these points, the author has carried out a histopathological study on human autopsied cases and obtained some new informations.

MATERIALS AND METHODS

Twenty-five cases of radiation pneumonitis were studied. Classifying the cases according to the basic diseases, 11 cases were carcinoma of the mamma, 4 lung cancer, 3 carcinoma of the esophagus, and 4 metastatic lung cancer, of which 2 were seminoma, 1 chorionepithelioma, and 1 reticuloendothelioma of the liver. The remaining 2 cases were reticulosarcoma and skin metastasis of carcinoma of the stomach. While all these cases received X-ray on the tumor, it was unavoidable that the adjacent lung would be radiated. The age, sex, basic disease are shown in Table I.

After the lung was fixed in formalin and macroscopic findings were recorded,
<table>
<thead>
<tr>
<th>Case No.</th>
<th>Age</th>
<th>Sex</th>
<th>Basic disorder</th>
<th>Radiation source</th>
<th>Total rad. dose (Right, Left)</th>
<th>Duration after 1st radiation (Right, Left)</th>
<th>Type of disease</th>
<th>Stage</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>25</td>
<td>♂</td>
<td>Chorionepithelioma</td>
<td>XR</td>
<td>6,000, 3,600</td>
<td>indistinct</td>
<td>A-E</td>
<td>early</td>
</tr>
<tr>
<td>2</td>
<td>69</td>
<td>♂</td>
<td>Carc. of esophagus</td>
<td>XR-Co</td>
<td>15,400, 3,000, 3,000</td>
<td>86D</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>41</td>
<td>♂</td>
<td>Carc. of mamma</td>
<td>XR</td>
<td>4,800, 13,500</td>
<td>35D, 123D</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>46</td>
<td>♀</td>
<td>Carc. of lung</td>
<td>Co-XR</td>
<td>12,600, 18,000, 13,900</td>
<td>270D</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>37</td>
<td>♂</td>
<td>Carc. of mamma</td>
<td>XR</td>
<td>3,600, 6,000</td>
<td>130D, 1.2Y</td>
<td></td>
<td>middle</td>
</tr>
<tr>
<td>6</td>
<td>39</td>
<td>♂</td>
<td></td>
<td></td>
<td>6,300</td>
<td>160D</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>59</td>
<td>♂</td>
<td>Reticuloendothelioma</td>
<td>Co</td>
<td>7,300, 6,000</td>
<td>330D, 220D</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>29</td>
<td>♂</td>
<td>Seminoma</td>
<td>XR</td>
<td>12,350, 10,500</td>
<td>250D</td>
<td></td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>60</td>
<td>♂</td>
<td>Carc. of lung</td>
<td></td>
<td>1,535, 5,400</td>
<td>60D</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>40</td>
<td>♂</td>
<td></td>
<td></td>
<td>15,000, 5,400</td>
<td>160D, 160D</td>
<td></td>
<td>late</td>
</tr>
<tr>
<td>11</td>
<td>49</td>
<td>♂</td>
<td></td>
<td></td>
<td>17,700, 14,700</td>
<td>300D</td>
<td></td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>36</td>
<td>♂</td>
<td>Carc. of esophagus</td>
<td>Co</td>
<td>3,250, 4,750, 3,750</td>
<td>83D</td>
<td>M</td>
<td>early</td>
</tr>
<tr>
<td>13</td>
<td>59</td>
<td>♂</td>
<td></td>
<td></td>
<td>2,400, 2,400, 3,750</td>
<td>90D</td>
<td></td>
<td>middle</td>
</tr>
<tr>
<td>14</td>
<td>43</td>
<td>♂</td>
<td>Reticulosarcoma</td>
<td>XR</td>
<td>2,400, 2,400</td>
<td>80D</td>
<td></td>
<td></td>
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<tr>
<td>15</td>
<td>55</td>
<td>♂</td>
<td>Carc. of mamma</td>
<td></td>
<td>11,500, 7,000</td>
<td>3.2Y, 300D</td>
<td></td>
<td></td>
</tr>
<tr>
<td>16</td>
<td>29</td>
<td>♂</td>
<td>Seminoma</td>
<td></td>
<td>11,700, 13,400</td>
<td>215D</td>
<td></td>
<td>late</td>
</tr>
<tr>
<td>17</td>
<td>32</td>
<td>♂</td>
<td>Carc. of mamma</td>
<td></td>
<td>10,800</td>
<td>250D</td>
<td>I-P</td>
<td></td>
</tr>
<tr>
<td>18</td>
<td>59</td>
<td>♂</td>
<td>Carc. of lung</td>
<td>XR-Co</td>
<td>9,200</td>
<td>1.1Y</td>
<td></td>
<td></td>
</tr>
<tr>
<td>19</td>
<td>53</td>
<td>♂</td>
<td>Carc. of mamma</td>
<td>XR</td>
<td>8,700, 6,000</td>
<td>2.3Y, 2Y</td>
<td>F-A(l)</td>
<td></td>
</tr>
<tr>
<td>20</td>
<td>51</td>
<td>♂</td>
<td>Carc. of stomach</td>
<td></td>
<td>9,000, 5,100</td>
<td>260D</td>
<td></td>
<td></td>
</tr>
<tr>
<td>21</td>
<td>37</td>
<td>♂</td>
<td>Carc. of mamma</td>
<td></td>
<td>13,800</td>
<td>1.6Y</td>
<td>F-A(d)</td>
<td></td>
</tr>
<tr>
<td>22</td>
<td>42</td>
<td>♂</td>
<td></td>
<td></td>
<td>15,500</td>
<td>6Y</td>
<td></td>
<td></td>
</tr>
<tr>
<td>23</td>
<td>40</td>
<td>♂</td>
<td></td>
<td></td>
<td>30,500</td>
<td>2.4Y</td>
<td></td>
<td></td>
</tr>
<tr>
<td>24</td>
<td>46</td>
<td>♂</td>
<td></td>
<td></td>
<td>indistinct</td>
<td>indistinct</td>
<td></td>
<td></td>
</tr>
<tr>
<td>25</td>
<td>49</td>
<td>♂</td>
<td></td>
<td></td>
<td>2,500, 17,500</td>
<td>3Y</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

paraffin slides were prepared. They were stained with Hematoxylin-Eosin stain, Elastica-Masson stain, Azan-Mallory stain, and van Gieson's stain. Where necessary, Gomori's silver impregnation, PAS stain, and PTAH stain were used. With frozen sections stained with Sudan III and its polarizing microscopic studies were carried out.

RESULTS

(I) Classification of type of disease

The classification of radiation pneumonitis into 4 stages by Engelstad or into 3 stages by Warren has ordinarily been used. However, these classifications are done mainly considering the time after radiation. In human cases, the method of radiation is variable and the period of radiations is also extended over a long time. Under such circumstances, the above-mentioned classification is often unreasonable. The author has classified this disease into 4 types from a pathomorphological standpoint on the degree of damages in tissue component of the lesion.

(A) Alveolar exudative type .......................... 11 cases
(B) Interstitial proliferative type ..................... 2 cases
(C) Mixed type ........................................... 5 cases
(D) Fibro-atelectatic type .............................. 7 cases
   (a) Localized form ................................. (2 cases)
   (b) Diffuse form (Collapse induration) ............ (5 cases)

The findings on each type will be briefly described.

(A) Alveolar exudative type:

This type is made of exudation caused by radiation and its organization, which occur in the alveoli. This finding is predominant in the disease. Edema, hyaline membrane formation, fibrin deposition and intraalveolar fibrosis are observed.

(B) Interstitial proliferative type:

The major finding in this type is fibrous thickening of the interstitial tissue including the alveolar septa. Corresponding to such changes, the elastic fibers will degenerate and rupture in that place.

The changes of alveolar epithelium are observed in both types. Proliferation and unique bizarre changes are seen.

(C) Mixed type:

When the above-mentioned changes exist in the same specimen and the major findings cannot be decided to belong in either type, it is classified in this group.

The above-mentioned 3 types can be classified into 3 stages; i.e. early, middle and late stages.
(D) Fibro-atelectatic type:

This type belongs to the late stage. It was seen in those who received 2 to 5 complicated series of radiation. A very characteristic finding is that the lungs are atelectatic, and abnormal proliferation of elastic fibers is observed on the alveolar wall which approaches together and shows hyaline thickening. Macroscopically, this is subdivided into localized and diffuse form according to the extent of lesions. In the latter form, the whole lung becomes contracted to a fist size. It can be called collapse induration from its characteristic appearance.

(II) Characteristic findings of the disease

The following findings are characteristic.

1. Intraalveolar changes
   (a) Intraalveolar edema

   Intraalveolar edema was observed in 13 of 25 cases. This change was frequently complicated in the early and middle stages. Especially, in the alveolar exudative type, it was always found. In general, the edematous fluid was thick. Frequently, a round gun shot picture or network-like pattern due to bubbles was observed.

   (b) Hyaline membrane formation

   In 7 of 25 cases, hyaline membrane formation was noticed. This was found mostly in the alveolar exudative type and was seen only in the cases with severe edema. Histologically, the hyaline membrane was found close to the alveolar duct and wall. It showed a membranous structure which was stained uniform with eosin. Generally, cellular infiltration and organization were not observed. When special staining was done, it was PAS positive, PTAH negative, Sudan III positive (negative double refraction by polarizing microscope) and stained red or violet with Azan-Mallory stain.

   Hyaline membrane was emphasized to be a characteristic finding of radiation pneumonitis by Warren and Spencer. However, opinions regarding this statement are not in agreement with later studies. Many reports are in agreement that this finding is found in many other lung affections, such as influenza, rheumatic pneumonitis, hyaline membrane disease in newborn, and Hamman-Rich syndrome, and is considered to be a relatively characteristic finding.

   The author studied the autopsied lung during the recent 5 years at our Department. Hyaline membrane of the lung was proved to occur in the following diseases, such as rheumatic fever, rheumatic endocarditis, rheumatoid arthritis, systemic lupus erythematosus, Raynaud’s disease, uremic pneumonitis, multiple myeloma, measles, tuberculosis and lung metastasis of chorionepithelioma. According to the literature, it was also found in pest, interstitial plasma cell pneumonia, virus pneumonia, poliomyelitis, irritant gas poisoning and oxygen or carbon dioxide poisoning (animal experiment).
Radiation Pneumonitis

(c) Fibrin deposition

Of 25 cases, 14 showed this change. Most of them were alveolar exudative type or mixed type. They include 4 carcinomas of the lung, 2 carcinomas of the esophagus, 3 metastatic lung tumors, 1 reticulosarcoma, and 4 carcinomas of the mamma. The cases with carcinoma of the mamma showed slight changes. This change was mostly found in those who received deep radiation therapy. In general, the lesion lacked infiltration of neutrophile leucocytes.

2. Changes of alveolar epitheliums

In the alveolar epithelium, regardless of various type of lesions, swelling and proliferation were both observed. Frequently, it assumed a bizarre form. Occasionally, the nuclei showed a very atypical form and sometimes a multinuclear giant cell with 2 to 3 nuclei was observed. The cytoplasm was also darkly stained with eosin and showed PAS positive. Proliferating alveolar epithelium desquamated and fell into the alveoli, and showed a tendency to fatty degeneration. Such a finding was observed remarkably in various places. A typical “Desquamative Pneumonie” in which a large-sized foam cell filled the alveolar space was not rarely observed. All examined 13 cases showed Sudan III positive reaction. In 6 cases (46%), double-refraction positive cholesterin was proved by a polarizing microscope (Cholesterin pneumonitis).4,24)

In the late stage, a gland-like metaplasia which resulted proliferation of the alveolar epithelium overlying the thickened alveoli was observed in 6 cases. This finding was often found in a fibrous lesion of the lung where satisfactory gas exchange did not occur.8)

3. Thickening of the alveolar septa (Interstitial pulmonary fibrosis)

Thickening of the alveolar septa was one of the most significant changes in radiation pneumonitis. The lesion appeared at the place where radiation had been given. In case of interstitial proliferative type, this lesion was predominant in the disease. There are, however, very few cases which were only limited to this change in human autopsied cases. Mostly, it accompanied the other exudative changes and they were found in almost all cases. When a detailed description was given, the early stage of the lesion began with congestion and edema. With the lapse of time, congestion disappeared, edema would gradually shift to fibrosis and proliferation of fibrils which showed positive silver impregnation occurred in the alveolar wall. Fibrillogenesis advanced with time. Transformation of collagen would occur and the thickening of alveolar septa was completed. The degree of fibrous thickening differs case by case, ranging from 2 to 3 times the normal to a markedly severe degree, such as found in Hamman-Rich syndrome. At this time, the local histiocytes and fibroblasts proliferated and participated in the completion of fibrosis. However, the characteristic finding was that proliferating cells were not many in comparison to fibrous thickening. Elastic fibers in thickened alveolar
septa and bronchiolar wall would degenerate, rupture or swell, which would take an irregular course. This was characteristic and would be helpful to microscopic examination.

The above-mentioned changes can be confirmed by animal experiment if it is done well. For instance, Jennings and Arden\textsuperscript{12}) radiated the lung of rats with a single dosage of 3,000 r and observed it periodically. The alveolar septa thickened edematously, at first. It was rich in fibrin. Then, it was followed with appearance of reticular fibers and gradually changed to collagen. After 6 months to 1 year, a relatively remarkable diffuse fibrosis was reported to occur. The author\textsuperscript{19}) also carried out animal experiments with rat and rabbit. In animals, a marked change could not be incited, which might be due to low sensitivity of endothelium of the alveolar capillary in comparison to human cases. However, in case of rabbit experiment, the same kind of changes as in human cases were confirmed in the alveolar septa in a few cases. Especially, in one case which received 10,000 r in divided dosage\* (500 r × 20 times continuous radiation) showed a marked change on the 140th day. In a fairly extensive area, a fibrous thickening of the alveolar septa was observed. Thickened alveolar septa showed 4 to 5 times the normal thickness at the most conspicuous place. It was stained uniformly with eosin, and relatively lacking in cellular proliferation. Rupture and tortuosity of elastic fibers were both recognized. In this case, the proliferation and bizarre change of alveolar epithelium, intraalveolar edema and fibrosis in the alveolar space and pleura were observed. In addition to that, ossification and calcification were found in fibrous lesion.

4. Changes of elastic fibers — especially on fibroatelectatic type

As previously described, elastic fibers in thickened alveolar septa and bronchiolar wall showed the change such as rupture and swelling, but the major change was degeneration, and tendency of proliferation was little.

In contrast to this finding, those changes which were observed in cases of fibroatelektatic type differed from the above change. In the alveolar septa of the atelectatic lung which approached together and blood vessels, a vigorous growth of elastic fiber was observed. These lesions looked like hyaline by H-E stain. It did not stain well with the collagen fiber staining. A compact proliferation of fibril which showed positive silver impregnation was noticed. Such abnormal growth of elastic fibers which occurs in radiation pneumonitis is not reported except the second case of chronic pulmonary fibrosis due to radiation by Voegt.\textsuperscript{22}) However, in the case studied by the author, 2 localized type, 5 diffuse type, 7 cases as a total were found. It was not very few, but probably overlooked so far.

\* Condition of radiation: 180 kV, 6 mA., Filter Cu 0.8 mm, Al 1.5 mm, HVL Cu 1.3 mm, FSD 20 cm, Dosage per minute 70.9 r/m., Radiation field: right unilateral lung, 2.5 \times 5 cm.
Voegt considered that the growing elastic fibers were a mixed mass of degenerated and destroyed elastic fibers and newly grown fibers. But detailed explanation of this mechanism had not been given.

There was study on abnormal growth of elastic fiber by Gillman et al. They studied elastic fibers which grew in various skin lesions from a standpoint of plastic surgeon. Fifteen kinds of staining were performed. Consequently, they thought both had different nature as these showed a different staining pattern from real elastic fibers. Basing their further studies on experimental dermatitis, they regarded that these elastic fibers were due to degeneration or metabolic abnormality of previously existing collagen fibers, and called them "elastotic degeneration of collagen" or "pseudoelastic fiber". As these were negative with collagen fiber staining, but stained in black fibril with silver impregnation, it corresponds well with the staining finding of fibro-atelectatic type proposed by the author. Gillman et al. did not mention on the lung lesions but observed it in radiation dermatitis. When histological resemblance is considered together, it may show the possibility that the abnormal elastic fiber which is seen in the fibro-atelectatic type is the pseudoelastic fiber which is due to elastotic degeneration of previously proliferating collagen due to radiation fibrosis. But fundamental studies on elastic fiber are still few. There are arguments against the conception of Gillman et al. Therefore, it leaves more studies to be made.

5. Changes of blood vessels

In blood vessels, fibrous thickening of intima, growth of elastic fiber of the media and proliferation of connective tissues around the adventitia were observed. These changes were remarkable in the late stage. Especially, the latter two changes were remarkable in fibro-atelectatic type. Cellular reaction was lacking in the fibrous thickening of the intima. It is characteristic that no participation of elastic fiber is seen and Zollinger called this "Intimafibrose" or "Endarteritis productiva".

6. Bronchial epithelium

In bronchial epithelium, increase of secretion of mucin, or metaplasia to squamous or cuboidal epithelium was seen. According to the literature, disappearance of cilia of the epithelium was the cause of stubborn cough. But in the author's cases, this point was not clear.

7. Complication of bronchopneumonia

This complication was found in 8 cases. When it was classified according to the stages, 4 belonged to the early stage (80%), 3 to the middle stage (45%) and 1 to the late stage (7.7%). Earlier the stage, the more frequent the complication.
Difference of reaction between X-ray and Co<sup>60</sup>

Twenty-five studied cases were classified according to the source of radiation.

(a) only Co<sup>60</sup> ..................................... 3 cases
(b) Co<sup>60</sup> with X-ray ................................. 6 cases
(c) only X-ray ............................................ 19 cases

The relationship between type of disease and source of radiation is shown in Table II. The source of radiation and type of disease did not show any significant correlation. The reason why the fibro-atelectatic type does not exist in the group radiated with Co<sup>60</sup> will be that they, belonging to the group having deep radiation, took a rapid course and died. It does not seem to be due to the difference of reaction. When it is considered that both X-ray and Co<sup>60</sup> will physically radiate a very similar ionizing radiant ray, it may be natural to accept this thought.

<table>
<thead>
<tr>
<th></th>
<th>X-ray only</th>
<th>Co&lt;sup&gt;60&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>A–E</td>
<td>8</td>
<td>3</td>
</tr>
<tr>
<td>M</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>I–P</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>F–A</td>
<td>7</td>
<td>0</td>
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<tr>
<td>Total</td>
<td>19</td>
<td>6</td>
</tr>
</tbody>
</table>

DISCUSSION

(I) Pathogenesis of radiation pneumonitis

When the lung receives a large dosage of radiation, epithelial tissue and mesenchymal tissue will both change. The changes which occur in the endothelium of alveolar capillary are most significant. Consequently, the permeability of blood elements will increase and alveolar spaces and interstitial tissues will both be invaded. It causes edema, hyaline membrane formation, fibrin deposition in the intraalveolar space and edematous thickening of interstitial tissue including alveolar septa (extravasation). These edema fluid is thick and occasionally contains fibrin, which differs from transudate observed ordinarily in pulmonary edema. These have a strong tendency to organization and fibrosis will gradually advance. In such a case, a differentiation of alveolar exudative type and interstitial proliferative type will be made depending on the degree of changes in the alveolar space or interstitial tissue. In general, the alveolar exudative type is seen mostly in the group with continuous radiation, while the interstitial proliferative type is seen in the group with intermittent radiation. This suggests that when endothelial cells are severely injured, intraalveolar
exudate is apt to occur, while when the injury is not severe, it remains as edema of the alveolar septa.\textsuperscript{1,15} At that time, it is observed that histiocytes and fibroblasts will participate in the completion of organization. Degeneration and rupture are also seen in the elastic fiber.

On the contrary, in the fibro-atelectatic type, abnormal growth of elastic fibers is seen, which seems to play an important role for the cause of atelectasis. In addition, this lesion appears like hyaline by H-E stain and does not stain well with collagen fiber staining. When these findings are reviewed, though it cannot be decided whether abnormal growth of elastic fiber is due to elastotic degeneration of collagen as reported by Gillman \textit{et al.} or not, it is very likely that it is a change due to abnormal metabolism of proliferated connective tissue. Though it was not recognized in human cases, in animal experiment, ossification was found in the fibroelastic lesion, which may be one of the proofs that abnormal metabolism would occur in the grown connective tissue.

\begin{table}[h]
\centering
\caption{Pathogenesis of Radiation Pneumonitis}
\begin{tabular}{|l|l|}
\hline
1. Capillary & \\
endothelium & Increase of permeability \\
\hline
2. Connective & Metabolic abnormality \\
tissue & \\
\hline
3. Alveolar & Metabolic abnormality \\
epithelium & \\
\hline
4. Bronchial epithelium & \\
\hline
\end{tabular}
\end{table}

Proliferation and swelling will occur in the alveolar epithelium. It often takes a characteristic bizarre form or shows a gland-like metaplasia. This has a tendency to desquamate and fall into fatty degeneration, while a part of it will contain cholesterol. This latter process may be due to abnormal metabolism.

In the bronchial epithelium, increase of mucous secretion or metaplasia is seen.

There is a problem whether to call this disease an inflammation or not. The author accepts the inflammation theory from the following points; 1) edema fluid is thick, and occasionally it contains fibrin and shows the nature of exudate, 2) participation of mesenchymal cells derived from tissue is seen in the secondary fibrotic area, 3) the reaction occurs in the connective tissue and blood vessel.
Henzi\textsuperscript{11}) takes a similar standpoint as the author. But considering the less cellular reaction in the fibrotic lesion, Zollinger\textsuperscript{26}) called this “Dysorose”, and Utsumi\textsuperscript{21}) contended the degeneration theory. Besides these theories on the pathogenesis of this disease, Kitamura and Kojima\textsuperscript{15}) proposed a theory of allergic pneumonitis which was based on the production of autoantibody.

(II) Classification of this disease

Engelstad\textsuperscript{9}) (1934) performed an extensive animal experiment with 116 rabbits and classified them into 4 stages, i.e. 1) initial stage, commencing 1 or 2 hours after irradiation and lasting 1 to 2 days, 2) the latent stage, with a duration of 2 or 3 weeks, 3) the main reaction, with marked degenerative and inflammatory changes. The acute inflammation has its maximum 1 to 2 months after the irradiation, and 4) the stage with principally regenerative changes, which gradually occurs. As a rule, the initial stage and the latent stage by Engelstad are not observed on human autopsy materials. All cases belong to the stage after the “main reaction”. From a histopathological study on human autopsied cases, Warren and Spencer\textsuperscript{25}) (1940) classified them into 3 stages, i.e. (1) acute, (2) late, and (3) combined acute and late (late with superimposed acute reaction). Henzi\textsuperscript{11}) classified this disease into 3 stages, i.e. (1) initial reaction (Frühreaktion), (2) specific damage was caused by irradiation (eigentliche Röntgenschädigung) and (3) late alteration (Spätveränderung). This is nearly similar to the 4 stages classification by Engelstad.

There are relatively few attempts to classify it from a morphological standpoint according to the place where the change is severe. Naming few of them, there are classification of alveolar exudative type and interstitial type by Kitamura et al\textsuperscript{15}), a classification which adds a mixed type to the previous one by Akazaki\textsuperscript{1}), a classification of alveolar edema type and alveolar wall edema type by Utsumi\textsuperscript{21}), and a classification by Mallory\textsuperscript{18}) who divided this disease into 2 groups, i.e. necrotizing pneumonitis and interstitial fibrosis in his classification of pulmonary fibrosis. Reviewing these classifications, there are 2 points in common; a group in which the major role is played by intraalveolar exudate and its organization, and the other is fibrous thickening of the interstitial tissue of the lung including alveolar septa.

As it has been described previously, the author classified this disease into alveolar exudative type, interstitial proliferative type, mixed type and fibroatelectatic type (a, localized form; b, diffuse form). The major finding in the alveolar exudative type is intraalveolar exudate and accompanying various changes, while in the interstitial proliferative type, edema of the alveolar septa and fibrous thickening play the major role. Both types may shift with each other amidst mixed type and may be explained as a different expression of a similar change.
Contrary to this, fibro-atelectatic type is a new proposal by the author. All belong to the late stage, which received a complicated radiation extending over 2 to 5 series. Histologically, the following characteristic finding is seen; the lung is atelectatic, abnormal growth of elastic fiber is seen in the alveolar wall, and does not stain well with collagen fiber staining. It differs entirely from the previously described late stages of alveolar exudative and interstitial proliferative type and is believed to have good reason to make it an independent type. The feature which is observed in fibro-atelectatic type is very rarely seen in other lung diseases. Similar findings were only seen in a case with healed infarction which was reported by Castleman and Mallory respectively. It is also unique as a type of pulmonary fibrosis.

\( III \) Diagnostic criteria of radiation pneumonitis

The following changes are named by the author as diagnostic criteria.

(a) Edematous or fibrous thickening of the alveolar septa. Rupture, degeneration and occasionally hypertrophy of the elastic fibers are also seen in that place.
(b) Swelling and proliferation of the alveolar epithelium, and formation of characteristic bizarre picture.
(c) Existence of thick intraalveolar edema, which is frequently accompanied with foam formation.
(d) Hayline membrane formation.
(e) Transition to intraalveolar and interstitial pulmonary fibrosis.
(f) In the late stage, formation of fibro-atelectatic area.
(g) Change of blood vessel.

The above-described individual changes may not be pathognomonic to this disease. However, when these changes are grouped together, the disease may be fairly accurately diagnosed.

CONCLUSION

Twenty-five autopsied cases of radiation pneumonitis have been studied and classified histopathologically into the following 4 types.

(A) Alveolar exudative type ......................... 11 cases
(B) Interstitial proliferative type ..................... 2 cases
(C) Mixed type ......................................... 5 cases
(D) Fibro-atelectatic type ............................. 7 cases
   (a) Localized form ................................. (2 cases)
   (b) Diffuse form (Collapse induration) ........... (5 cases)

These types are divided into 3 stages, i.e. early, middle and late stages.

(A) Alveolar exudative type: major changes are intraalveolar exudate and its organization. Edema, hyaline membrane formation, fibrin deposition and
intraalveolar fibrosis are observed.

(B) Interstitial proliferative type: This type is characterized by fibrous thickening of interstitial tissue including alveolar septa, and corresponding to this change, rupture and degeneration of elastic fiber are observed.

The change of alveolar epithelium can be seen in both types.

(C) Mixed type: The changes of (A) and (B) are mixed. It is made independent when the major change cannot be decided.

(D) Fibro-atelectatic type: In this type, abnormal growth of elastic fiber and atelectasis of the lung are remarkable. These are subdivided into local form and diffuse form. Both belong to the late stage. It is a unique form as a final phase of radiation pneumonitis and also a specific type of pulmonary fibrosis.

There is no difference of reaction between X-ray and Co⁶⁰ irradiation. In regard to the pathogenesis of this disease, the increase of capillary permeability of the alveolar wall will play the most important role. In addition to it, the lesion is decorated by abnormal metabolism of alveolar epithelium and the new grown connective tissue.

Finally, the diagnostic criteria of this disease have been discussed.

References

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Radiation Pneumonitis

Fig. 1. Hyaline membrane formation. In contact with the alveolar duct, a hyaline membrane is stained uniformly with eosin.

Fig. 2. Change of alveolar epithelium. Cytoplasm and nuclei will both remarkably increase its size and show a unique bizarre picture.

Fig. 3. Cholesterin pneumonitis. In the alveolar epithelium which shows fatty degeneration, positive double-refractive cholesterin is proved by polarizing microscope.

Fig. 4. Intraalveolar fibrosis with rupture and degeneration of elastic fiber. Left, H-E stain. Right, Elastica-Masson stain.

Fig. 5. Fibrous thickening of alveolar septa (1). In comparison with the thickening of alveolar septa, proliferation of cellular elements is relatively few.

Fig. 6. Fibrous thickening of alveolar septa (2). Fibrous thickening of alveolar septa is remarkable. Left, H-E stain. Right, Gomori's silver impregnation.
Fig. 7. Collapse induration. The right lung is contracted to a fist size and shows a unique external appearance.

Fig. 8. Fibro-atelectatic type (1). H-E stain. In general, the lungs are atelectatic. Proper alveoli are hard to identify and the alveolar wall appears like hyaline.

Fig. 9. Fibro-atelectatic type (2). Elastica-Masson stain. Abnormal growth of elastic fiber is very characteristic.

Fig. 10. Fibro-atelectatic type (3). Left, Gomori's silver impregnation. A thick growth of fine argyrophilic fibrils is observed. Right, Elastic-Masson stain. The change of blood vessel is remarkable.

Fig. 11. Animal experiment (1). Fibrous thickening of alveolar septa and changes of epithelium are observed.

Fig. 12. Animal experiment (2). Left, Elastica-Masson stain. Degeneration of elastic fiber. Right, H-E stain. Ossification in fibrous area is shown.