Complete Atrioventricular Block Following Radiation Therapy for Malignant Thymoma

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Complete atrioventricular block following radiation is very rare. We present a case which developed after radiation therapy for malignant thymoma. The etiology of conduction disturbances due to radiation is unknown. In our case, serial electrocardiograms showed stepwise progression of the conduction disturbance, and His bundle electrocardiograms revealed new prolongation of the H-V interval. Endomyocardial biopsy specimens demonstrated occlusion in small arteries and diffuse degenerative changes in the myocardium. We therefore attributed the complete atrioventricular block in our patient to secondary damage to the conduction system, caused by radiation-induced occlusive changes in the small arteries supplying the conduction system.

Key words: Complete atrioventricular block, Radiation therapy, Malignant thymoma, Endomyocardial biopsy

Recently some cases of radiation-induced heart disease have been reported. Most have been pericarditis or ST-T changes on electrocardiogram. Conduction disturbances following radiation therapy are rare. We present a case of complete atrioventricular block after radiation therapy for malignant thymoma, and discuss the etiology of this particular complication.

CASE REPORT

A 64-year-old man, who had previously been free from chest pain, consulted a local hospital because of dyspnea in Nov. of 1987. An echocardiogram revealed massive pericardial effusion. An electrocardiogram (Fig. 1-a) showed left axis deviation and frequent short runs of ventricular premature beat, but no evidence of atrioventricular block. The diagnosis of malignant thymoma was confirmed by CT of the thorax and pericardiocentesis. Combination chemotherapy with cyclophosphamide, vincristine, procarbazine and prednisolone was given as a single course in doses of 1900 mg, 3 mg, 1960 mg and 770 mg, respectively.

He was referred to our hospital for radiation therapy on Jan. 11, 1988. The admission chest x-ray showed significant enlargement of the cardiac silhouette. CT of the thorax (Fig. 2) demonstrated a large mass in the anterior mediastinum and massive pericardial effusion. During the period from Jan. 22 to Apr. 15 he received radiation therapy, delivered by a 1-MeV unit to exposed anterior and posterior fields. The radiation was applied to the field encompassing the entire heart and the mediastinum at a rate of 1.5 Gy per day, 5 days a week for 4 weeks, and then to the field encompassing only the tumor at a rate of 2 Gy per day, 5 days a week for 3 weeks. The total tumor dose was 60 Gy. The size of the mass decreased significantly with this treatment, and he was discharged.

He noticed discomfort in the anterior chest in May, 1988. Because a 24-hour ambulatory electrocardiographic recording confirmed frequent ventri-
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Fig. 1. Electrocardiograms at first admission to our hospital (a), at his family clinic (b), and at onset of complete atroventricular block (c).

Fig. 2. CT of the thorax on the first admission showing a large mass in the anterior mediastinum (a) and massive pericardial effusion (b).

cular tachycardia, he again entered our hospital. Various antiarrhythmic drugs were given without noticeable effect for 2 weeks, till the ventricular tachycardia subsided spontaneously. We then attempted to provoke ventricular tachycardia during an electrophysiological study, but failed. A His bundle electrocardiogram (Fig. 3-a) showed normal A-H and H-V intervals of 98 and 50 milliseconds, respectively.

Resection of the malignant thymoma was performed on Aug. 18. The left brachiocephalic vein, the superior vena cava and a smaller part of pericardium invaded by the tumor were completely resected, and the great vein was reconstructed using an artificial graft. Microscopic examination of the resected specimen showed changes characteristic of a predominantly epithelial thymoma. The postoperative course was satisfactory. After discharge he attended his family clinic, and without any antiarrhythmic drugs remained free of ventricular premature beats. He was relatively well, but the electrocardiogram recorded on Oct. 15 (Fig. 1-b) demonstrated complete right bundle branch block for the first time.

On Dec. 3, 1988 he suddenly experienced shortness of breath while walking. He came to the
Fig. 3. His bundle electrocardiograms (HBE) before (a) and after (b) complete atrioventricular block. The H-V interval was elongated from 50 to 60 milliseconds after the heart block. II = lead II of the standard lead electrocardiogram.

Fig. 4. Echocardiograms after complete atrioventricular block showing good contraction of the left ventricular wall.
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Emergency room at our hospital the next morning. The electrocardiogram on arrival (Fig. 1-c) demonstrated complete atrioventricular block at a ventricular rate of 48, in addition to complete right bundle branch block and left axis deviation. Immediately after temporary pacemaker insertion, he experienced complete relief. He remained in sinus rhythm until he entered the CCU. An x-ray film of the chest disclosed neither cardiac enlargement nor interstitial edema. An echocardiogram (Fig. 4) revealed good contraction of the left ventricular wall. Laboratory findings on admission, including angiotensin converting enzyme level, were normal, with the exception of a platelet count of 97,000 per mm$^3$. Viral antibody titers on paired serum were not significantly increased.

Right-sided cardiac catheterization was performed on Dec. 6, 1988. An electrode catheter was introduced from the right femoral vein and advanced into the right ventricle. Then the catheter was slowly withdrawn to the right atrium, confirming the absence of split His potential. The H-V interval on a His bundle electrocardiogram (Fig. 3-b) was 60 milliseconds. The prolongation had not been detected 6 months earlier. Endomyocardial biopsy specimens from the right ventricle (Fig. 5) revealed marked degenerative changes in myocytes. Myocytolysis and a scarcity of myofibrils were seen throughout. Disarrangement of myocytes was also severe. To some extent interstitial fibrosis and fatty infiltration were seen. The lumen of some small arteries was completely obstructed due to vacuolization of the media. But the biopsy specimens were negative for thymoma cells and showed no findings compatible with sarcoidosis. Coronary angiography was not performed because the patient was allergic to iodine.

A permanent pacemaker was implanted on Dec. 15, 1988. Seven days later complete atrioventricular block appeared again and pacemaker rhythm persisted. Thallium-201 myocardial imaging (Fig. 6) disclosed diffuse and irregular perfusion defects except in the lateral wall of the left ventricle. The distribution of perfusion defects did not correlate with any segments supplied by coronary arteries. Cardiac blood pool imaging showed good contraction of the left ventricular wall. The calculated ejection fraction was 68 percent.
DISCUSSION

The heart was formerly thought to be very radioresistant, but today some attention has been focused on radiation-induced cardiac damage. Most patients had received more than 40 Gy to the area of the heart. Electrocardiographic abnormalities, commonly ST-T changes, have been observed after radiation therapy. But complete atrioventricular block following radiation therapy is very rare. To our knowledge, only seven cases have been reported (1-6). These cases and the current one are summarized in Table 1.

Electrophysiological studies were performed in two of the previously reported cases, but performed only either before or after heart block. In one case, heart block was demonstrated to be above the level of the bundle of His when a permanent pacemaker was implanted (4). In another case, the His bundle electrocardiogram, recorded before complete atrioventricular block appeared, revealed prolongation of the H-V interval (5).

In our patient we recorded a His bundle electrocardiogram twice, and could document the appearance of prolongation of the H-V interval. A 12-lead electrocardiogram showed a complete right bundle branch block pattern and left axis deviation before the development of complete atrioventricular block. The morphology and axis of the QRS complexes were the same as those seen during the heart block. This suggested that the subsidiary pacemaker arose proximal to branches of the left posterior hemifascicle. The rate of ventricular escape beats during complete atrioventricular block was slow, 48 beats per minute. This suggested that the subsidiary pacemaker was located at the His bundle or distal to it. Moreover, the only new abnormal finding after complete atrioventricular block was prolongation of the H-V interval. Therefore, we postulated that a portion of the complete atrioventricular block was attributable to the His bundle or proximal left posterior hemifascicle.

It has been reported previously that pathological findings in radiation-induced heart disease were disarrangement and hypertrophy of myocytes, porosity of myofibrils, various sizes of nuclei, and mild interstitial fibrosis (7, 8). These findings are similar to those of our patient.

Of primary importance in the diagnosis of radiation-induced myocardial damage, is the correlation of the damaged area with the irradiated region. Thallium-201 myocardial scintigraphy in our patient showed a diffuse perfusion defect which could not be explained by coronary artery disease. A 1-MeV x-ray unit was administered to the whole heart and the mediastinum in the first half of treatment, then the irradiated region was restricted to only the tumor in the latter half. The distribution of the perfusion defect in the myocardial scintigram corresponded to the region irradiated throughout the therapy (a total dose of 60 Gy).

Our patient received chemotherapy but it is unlikely that these agents, administrated at very low doses, contributed to the myocardial disease (9). Our patient showed no signs suggesting myocarditis. Coronary heart disease cannot be completely ruled out because a coronary angiogram was not performed. But he had not experienced any previous attacks of angina, and good contraction of left ventricle was demonstrated by echocardiography

Table 1. Summary of reports of complete atrioventricular block following radiation therapy.

<table>
<thead>
<tr>
<th>Report</th>
<th>Age at treatment (yr)</th>
<th>Interval (yr) to onset</th>
<th>Radiation dose (Gy)</th>
<th>Basal disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rubin (1963)</td>
<td>44</td>
<td>23</td>
<td>no record</td>
<td>Breast cancer</td>
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<td>Tzivoni (1977)</td>
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<td>18</td>
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<td>Breast cancer</td>
</tr>
<tr>
<td>Cohen (1981)</td>
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<td>23</td>
<td>37</td>
<td>Breast cancer</td>
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<tr>
<td>Kereiakes (1983)</td>
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<td>16</td>
<td>40</td>
<td>Hodgkin’s disease</td>
</tr>
<tr>
<td>Nishizawa (1987)</td>
<td>33</td>
<td>16</td>
<td>40</td>
<td>Hodgkin’s disease</td>
</tr>
<tr>
<td>Nakao (1989)</td>
<td>63</td>
<td>&lt; 1</td>
<td>60</td>
<td>Malignant thymoma</td>
</tr>
</tbody>
</table>

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and cardiac blood pool imaging. Although thallium-201 myocardial imaging revealed a diffuse perfusion defect, the distribution was not consistent with any segments supplied by coronary arteries. We therefore believe that complete atrioventricular block in our patient was a sequelae of previous mediastinal irradiation.

The interval from radiation therapy to the development of complete atrioventricular block ranged 6 to 23 years in previous reports (Table 1). The reason for the relatively early onset in our case was not clear. The possible explanations were as follows: (a) advanced age, (b) preexistent left axis deviation, (c) difference in mechanism of radiation-induced conduction disturbance. Advanced age would be an especially important factor. Several studies have shown that electrocardiographic evidence of left axis deviation (10), presumably due to left anterior hemiblock, right bundle branch block and left bundle branch block (11) increases with age. The early onset in our case was probably related to the greater vulnerability of the conduction system as compared with other younger cases. On the other hand, Patri et al (12) reported that a 65-year-old man manifested Mobitz type II atrioventricular block 11 months after radiation therapy. Like our case, this case manifested high degree atrioventricular block within 1 year of radiation therapy. In the other cases, intervals were all more than six years and up to 23 years in two cases. Moreover, pathological findings showed only mild myocardial fibrosis in our case in contrast in marked fibrosis of the myocardium and conduction system in a previous case in which complete atrioventricular block developed 11 years after irradiation (4). This evidence suggests that radiation-induced conduction disturbances may be classified into an early-onset type and a late-onset type. The pathogenesis of the two types may be different.

There are two opinions on the etiology of conduction disturbances due to radiation (3). One is that secondary damage to the conduction system results from damage to vessels or ischemia. Another is direct damage to the conduction system. Cohen et al (4) reported a postmortem study of radiation-induced complete atrioventricular block in Hodgkin's disease. Microscopic examination revealed marked fibrosis of the atrioventricular node with marked cytoplasmic vacuolization, necrosis of muscle cells, myocardial fibrosis and narrowed arterioles.

Our case showed us some intriguing evidence to consider in the etiology of radiation-induced heart block. In our patient, presumed left anterior fascicular block existed prior to radiation therapy, and he developed complete right bundle branch block within seven months of radiation therapy and complete atrioventricular block four months later. Moreover, the endomyocardial biopsy specimens revealed complete occlusion in some small arteries. Blood supply to the right bundle branch is single, while the blood supply to the posterior fascicle of left bundle branch and the His bundle is dual (13). The stepwise and rapid progression of the conduction disturbance and histological findings suggested that damage to the conduction system had gradually spread from the portion most sensitive to ischemia to an area less sensitive. Furthermore, it was unlikely that marked fibrosis existed in the conduction system, because myocardial fibrosis was mild. In conclusion, we attributed the complete atrioventricular block in our patient to secondary damage to the conduction system, which had been caused by radiation-induced occlusive changes of the small arteries supplying the conduction system.

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REFERENCES