Rheumatoid Nodules of the Lung in a Patient with Palindromic Rheumatism

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We report a case of rheumatoid nodules of the lung seen in a patient with palindromic rheumatism. A 54-year-old man with palindromic rheumatism was admitted for evaluation of three nodules in the right upper lobe on chest roentgenogram. Wedge resection was performed for the purpose of confirmative diagnosis and treatment. Histology of these lung lesions revealed palisaded histiocytic cells surrounding a layer of central necrosis, which were considered to be characteristic findings of rheumatoid nodule. Such a case is extremely rare. To our knowledge, only one other case has been reported before in the literature.

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Key words: preceding lung lesion, immunohistochemical study

Introduction

Palindromic rheumatism (PR) was described and named by Hench and Rosenberg in 1941 (1). The typical clinical features are as follows: 1) very rapid appearance and disappearance of an attack of arthritis in one or more joints, 2) duration of attack of only a few days, 3) irregular intervals of recurrence, 4) absence of laboratory data suggesting rheumatoid arthritis (RA), such as rheumatoid factor, 5) absence of radiographic abnormalities and functional disturbance of joints. Recently, it has been generally accepted that PR is a pre-stage condition of RA or a disease belonging to the category of an atypical type of RA, because PR often evolves into true RA (2). We report on an extremely rare case of multiple rheumatoid nodules of the lung, which appeared prior to the onset of PR.

Case Report

A 54-year-old Japanese male began to suffer from attacks of arthritis from February 1989. The attack began abruptly at irregular intervals in one or more joints, and then terminated spontaneously within a few days without a residue of functional disturbance. On May 1989, he underwent a medical examination. Both RA test and C-reactive protein were positive (each 1+), however morning stiffness, subcutaneous nodules and radiographic changes of joints were not found. His recurrent arthritis was diagnosed as PR, because the clinical picture was consistent with PR except for rheumatoid factor. Local and systemic treatments with anti-inflammatory drugs, which were given only during an attack, were started. In December 1989, three abnormal nodules on chest roentgenogram were incidentally pointed out at the time of a health check-up. He was admitted to Sapporo Medical College Hospital on January 1990 for evaluation of those lung lesions. He was free from respiratory symptoms. Physical examination on admission revealed no significant abnormal findings including clinical signs suggestive of RA. Laboratory data disclosed the following values; C-reactive protein (1+), erythrocyte sedimentation rate (21 mm/h), fibrinogen (499 mg/dl), RA test (3+), RAHA (320×), ANF (−), IgG (904 mg/dl), IgA (423 mg/dl), PPD (15 × 20 mm in diameter of erythema) and other laboratory analyses (complete blood count, urinalysis, biochemistry, complements and tumor markers) were within normal limits. Sputum cytology was class I. Bacterial cultures of sputum were negative (Table 1). A chest roentgenogram disclosed three nodules, about 10 mm in diameter, in the right upper and middle lung fields (Fig. 1). CT demonstrated three well-defined rounded nodules without cavity, calcification and satellite lesions in the subpleural regions of right S2 and S3 (Fig. 2). Neither pleural effusion nor swollen lymph nodes were found. A retro-
Table 1. Laboratory Data on Admission

Peripheral blood
- RBC: $470 \times 10^6$/mm$^3$
- Hb: 14.8 g/dl
- Ht: 44.1%
- PI: $33.5 \times 10^4$/mm$^3$
- WBC: 7,700/mm$^3$

Serological exam.
- CRP: (1+)
- RA: (3+)
- RAHA: 320x
- ANF: (-)
- IgG: 904 mg/dl
- IgA: 423 mg/dl
- IgM: 153 mg/dl
- C3: 76 mg/dl
- C4: 43 mg/dl

Urinalysis
- glucose: (-)
- protein: (-)
- urobilinogen: (±)
- occult blood: (-)
- Fibrinogen: 499 mg/dl
- ESR: 21 mm/h
- PPD: 20 x 15 mm

Biochemical exam.
- GOT: 11 IU/l
- GPT: 9 IU/l
- LDH: 242 IU/l
- γ-GTP: 17 IU/l
- ALP: 121 IU/l
- Ch-E: 265 IU/l
- T. Bil.: 0.6 mg/dl
- T. chol.: 166 mg/dl
- T. G.: 89 mg/dl
- BUN: 17 mg/dl
- Crea.: 0.9 mg/dl
- UA: 5.6 mg/dl
- Na: 140 mEq/l
- K: 4.4 mEq/l
- Cl: 104 mEq/l
- T.P.: 6.9 g/dl
- A/G: 1.16

Tumor markers
- CEA: 2.0 ng/ml
- SLX: 17.8 U/ml
- SCC: 1.0 ng/ml
- NSE: 5.6 ng/ml
- TPA: 58.4 U/l

Fig. 1. Chest roentgenogram on admission shows multiple nodules (arrows) in the right upper and middle lung fields.

Fig. 2. CT demonstrates three well-defined rounded nodules in the subpleural regions.

cutaneous biopsy or by aspiration cytology, wedge resection of all nodules was performed for not only the differential diagnosis but also the treatment. Histology of each nodule revealed that the necrotic center was surrounded by a palisade of elongated histiocytic cells and a granulation tissue which consisted of numerous lymphocytes with scattered lymph follicles and other various inflammatory cells. In the outer zone of the granulation tissue, a proliferation of small blood vessels with wall thickness were found (Fig. 3 A,B). These were characteristic findings of rheumatoid nodules. On immunohistochemical study, immunostainings for UCHL1 (pan T cell), L26 (pan B cell) and CD4 were performed. CD4 positive T cells were dominant in the granulation tissue.

From a few days after admission, symptoms of arthritis which had previously disappeared within a few days came to persist, and morning stiffness developed. Other clinical signs of RA such as subcutaneous rheumatoid nodules and radiographic changes of bones and joints were not found. These clinical symptoms suggested that PR had evolved into the initial stage of RA on ad-
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The present case supports the above reports that seropositive PR tends to evolve into RA.

Rheumatoid nodules of the lung occur most frequently in men with a long standing history of RA and cigarette smoking, a high titer of rheumatoid factor and subcutaneous nodules. They may wax and wane in concert with the activity of the arthritis (8). The radiographic features show a well-defined rounded nodule, which is usually multiple and occasionally has a cavity, ranging from microscopic to several centimeters in diameter. Rheumatoid nodules tend to be located in the bilateral upper and middle lung fields and are generally in subpleura and interlobular septa. As an extremely rare instance, a case of an endobronchial rheumatoid nodule was reported by Johnson et al (9). Since the radiographic findings of the nodules are nonspecific, it is difficult to distinguish them from metastatic lung tumor, tuberculoma and abscess. Therefore, histological studies are indispensable for their diagnosis, especially in a case where these nodules have preceded the onset of rheumatic diseases (RA, PR). In the present case, as malignancy was not ruled out radiographically and neither a histological nor cytological diagnosis was made through echo-guided percutaneous biopsy nor aspiration cytology, wedge resection was performed for the purpose of not only the differential diagnosis but also the treatment.

Rheumatoid nodules of the lung are identical in structure to those of subcutaneous lesions. The histology of these nodules is characterized by a palisade of elongated histiocytic cells surrounding a layer of central necrosis, which in turn is surrounded by a vascularized granulation tissue containing a chronic inflammatory infiltrate (10, 11). Histological study of our resected specimens also disclosed the same findings.

Despite various hypotheses such as immunological mechanism, disturbance of circulation due to vasculitis, tissue damage by cytotoxic agents, etc., the pathogenesis of these nodules remains obscure. Immunohistochemical analysis, which has recently been applied by many investigators (12-14) to clarify the pathogenesis of such nodules, revealed important findings. Deposition of immune complexes was found in the central necrotic zone. The palisaded cells were found to belong to the monocyte-macrophage lineage based on positive staining for HLA-DR, CD14 and OKM1. Lymphocytes infiltrating into the granulation tissue were mainly T cells. CD4 positive cells were superior in number to CD8 positive cells. On the basis of these immunological findings, Ziff (15) proposed the following hypothesis. The process of the nodule formation consists of a series of immunoreactions; 1) local pooling of rheumatoid factor immune complexes due to trauma to small blood vessels at points of pressure, 2) activation and mobilization of macrophages by immune complexes, 3) production of tissue necrosis by cytotoxic agents and chemotaxis of chronic inflammatory cells by monokines, each released from

Fig. 3. (A) Histological features reveal several layers centering around the necrosis (H.E. staining; x2). (B) The necrotic center is surrounded by a palisade of histiocytic cells and a dense diffuse cellular infiltration (H.E. staining; x100).

**Discussion**

Among lung involvements associated with collagen vascular diseases, rheumatoid nodule is a well-described manifestation of RA, but is uncommon in Japan (3, 4). In particular, such a case of rheumatoid nodule of the lung seen in a patient with PR is extremely rare. In addition to the present case, only one other case (5) has been reported before in the literature. Furthermore, the present case shows the singularity that these lung nodules preceded the onset of PR.

As described in the introduction, it is generally said that patients with PR are seronegative for rheumatoid factor, however some controversy remains. In a review of 15 patients with PR who subsequently evolved into RA by Wajed et al (6), 9 patients (60%) showed a high titer of rheumatoid factor. Among 90 cases with PR reported by Mattingly et al (7), 41 cases out of 45 who were seropositive for rheumatoid factor developed RA.
activated macrophages.

In the present case, it was not difficult for us to diagnose the nodules as rheumatoid nodules due to the typical histological features, and the results of immunostaining supported this diagnosis. Especially in a case without typical features, immunohistochemical study may offer some significant information for the histological diagnosis.

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References