Case Report

Sarcoidosis with Multiple Calcification

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Sarcoidosis, having a twenty-nine years of clinical course, associated with multiple calcified deposits in neck, mediastinum, liver, spleen, kidney, abdominal lymphnodes and lung was reported. Calcified opacity, which was firstly detected during initial two years on plain chest and abdominal x-ray films, increased in calcified mass insidiously. Though, the examination on this admission failed to reveal pathogenesis of multiple calcification, immunological derangement seemed to initiate and promote the calcification.

Key Words: Sarcoidosis, Multiple calcification

Although pathogenesis of sarcoidosis, non caseating granuloma formation in body elsewhere histopathologically, was yet unknown, an immunological tool like bronchoalveolar lavage (BAL) could afford us that specific lymphocyte subpopulation are taking some role in the development of sarcoidosis¹⁾. As a systemic disorder, sarcoidosis was associated with many complications, among which calcification was mostly reported in mediastinal lymphnodes²⁾ and/or urinary tract³⁾.

We experienced multiple calcification in neck, mediastinum, liver, spleen, kidney, abdominal lymphnodes and lung in a case having a long history of sarcoidosis.

CASE REPORT

She first noticed blurred vision in 1956, when she was undertook neck lymphnode biopsy and diagnosed having sarcoidosis. She was followed by nearby physician with no medication for the initial 26 years and with short-acting steroid injection twice or three times a year for the late two years because of wheezing episode. Three years prior to admission she began to notice epigastralgia. She

was admitted on February 14, 1984 for precise evaluation of her disease. On admission, she was apparently well and complaining of no arthralgia, no dry mouth and no dry eye. A physical examination revealed: body temperature 36.3°C, body weight 47kg, height 153cm, heart rate 74 beats/min. and regular, respiration rate 16/min., blood pressure 132/70mmHg, inspiratory fine crackle on bilateral upper lung field. There were no struma, no hepatomegaly, no splenomegaly and no palpable cutaneous lymphnodes. The electrocardiogram was normal. The plain chest x-ray film disclosed bilaterally distributed reticulo-linear shadows with innumerable small calcified nodules (Fig. 1) and chest x-ray tomogram, computed tomogram revealed no hilar lymphnode enlargement. Plain abdominal x-ray film (Fig. 2) and abdominal computed tomogram (Fig. 3) showed multiple calcifications distributed in liver, spleen, kidney and abdominal lymphnodes. Laboratory data showed: erythrocyte sedimentation rate 72mm/hour, C-reactive protein 4+, fibrinogen 527mg/dl, peripheral white blood cell 7600/mm³ with 63% neutrophil, 23% lymphocyte, 13% monocyte and 1% eosinophil, hemoglobulin

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Fig. 1. Plain chest x-ray film taken on February 14, 1984. There are innumerable calcified opacity.

12.4g/dl, red blood cell $464 \times 10^4/\text{mm}^3$, platelet $38.9 \times 10^4/\text{mm}^3$. Total protein was 7.9g/dl with 46.1% albumin, 3.8% α_1 globulin, 12.9% α_2 globulin, 8.1% β globulin and 29.1% γ globulin. The lactate dehydrogenase (LDH) was 330IU/ml, glutamate aspartate aminotransferase (GOT) 18IU/l, glutamate pyruvate transaminase (GPT) 19IU/l, alkaline phosphatase (ALP) 525IU/l, leucine aminopeptidase (LAP) 97IU/l, glutamyl transpeptidase (γ GTP) 92IU/l, choline esterase 4.55IU/l. Serum sodium was 138mEq/l, potassium 4.5mEq/l, calcium 4.5mEq/l, magnesium 0.7mg/dl, phosphorus 3.2mg/dl. The BUN was 15mg/dl and creatinine 0.7mg/dl. Serological data disclosed IgG 2,300mg/dl, IgA 505mg/dl, IgM 370mg/dl, C3 159mg/dl, C4 22mg/dl, negative rheumatoid reaction, and negative LE test, negative coombs test, negative reaction to dinitrochlorobenzene, cold agglutinin 512x, thyroid test 25600x, microsome test 25600x, antiDNA antibody 14.7u/ml (Normal range is less than 15u/ml), positive PPD skin reaction $10 \pm 15/45 \pm 35$ mm. There were 80.5% T cell and 10.0% B cell in peripheral blood and mitogenic response to PHA was 55,130cpm. (451.9SI), ConA

Fig. 2. Plain abdominal x-ray film taken on February 14, 1984. There are innumerable calcified opacity.

Fig. 3. Abdominal computed tomogram taken on March 12, 1984.

17,743cpm. (145.4SI) and PWM 2,981cpm (24.4SI). Serum angiotensin converting enzyme was 23.8U/ml, lysozyme 13.4mg/dl and β_2 microglobulin $3.0 \mu\text{g/l}$. Respiratory function test showed 2030ml of vital capacity (%VC 80%), 1530ml of forced expiratory volume in one second

(FEV1.0% 77.6), residual volume 1,000ml (RV/TLC 33.3%) and diffusion capacity (DLco) 12.8ml/min./mmHg. Blood gas analysis were 75.5mmHg of Pao₂, 43.9mmHg of Paco₂ and 7.435 of PH. Gastrofiberscopic study in 8th hospital day revealed diffuse small, wide-based nodules on stomach mucosa and biopsied specimen disclosed noncaseating granuloma associated with giant cell formation as shown in figure 4. No acid bacilli was found on Ziel-Nielsen stained biopsied specimen and culture of gastric juice did not yield acid fast bacilli. Gallium-citrate scintigraphy revealed abnormal accumulation of isotope in neck and lung lesion. Therefore, transbronchial lung biopsy via flexible bronchofiberscope (Olympus type 1T10, Japan) was performed on the next step, but only inappropriate materials were obtained. Bronchoalveolar lavage undertaken simultaneously, revealed 3.5×10^6 N.C.C. and 36.0% lymphocyte, 57.0% alveolar macrophage, 7.0% neutrophil, with lymphocyte subpopulation of 71.8% OKT4 cell and 9.8% OKT8 cell and 26.4% OKT1A1 cell. Culture of BAL fluids also showed no growth of acid fast bacilli. Lymph node biopsy in left neck region showed noncaseating granuloma in association with giant cell formation. There was no keratoconjunctivitis or uveitis supporting of ocular sarcoidosis or Sjogren's syndrome, however, Schirmer test and rose-bengal test were positive. Because of these findings, we studied submandibular gland with contrast medium which

revealed slight apple tree appearance of ducts and performed buccal mucosal biopsy resultant with scarce lymphocyte infiltration which findings failed to reveal existing of Sjogren's syndrome. There were negative anti-SSA and anti-SSB antibody. There were a few fine granular calcification in thyroid gland upon echogram and normal technetium image of thyroid gland. Finger bone x-ray film disclosed cystic bony lesion, which was suggesting of sarcoid involvement, in distal end of the proximal and proximal end of the distal phalanges. Concerning parathyroid and thyroid function, parathyroid hormone-C was 0.1 ng/ml, parathyroid hormone-N was 71 pg/ml, parathyroid hormone-M 1.3 ng/ml, 25-OH vitamin D 8.8 ng/ml (Normal range is 14-42ng/ml), calcitonin 42pg/ml, T4 6.3 µg/dl (6.1-12.1 µg/dl), TSH 4.4u/ml (normal value is less than 10u/ml), normal response of thyrotropin releasing hormone (TRH) test and normal response of Howard Ca tolerance test. Daily urinary calcium levels were from 2.1mg to 6.7mg. Thyroid gland biopsy could not be allowed to perform. Taken together, the accelerated ESR, high positive CRP, elevated ratio of OKT+ positive cell in bronchoalveolar lavage fluids and sarcoid lesion distributed at least in stomach, neck lymph node, probable in lung and salivary gland, prednisolone treatment was started with a dose of 30mg per alternate days and she was discharged. One month later, however, she withheld steroid medication because of developing of lumbago. All the while, it was no fever and no exacerbation of chest x-ray film.

Fig. 4. Stomach biopsied-specimen obtained on February 22, 1984 showing noncaseating granuloma with Langhans-typed giant cells. Hexatoxylin-Eosin stain, 400x.

DISCUSSION

Since she has been diagnosed to suffer from sarcoidosis, it passed twenty-nine years without steroid treatment. Plain chest x-ray film and abdominal film taken initial two years revealed multiple calcified opacities. Around that time she noticed no episode of thirst sensation, polyuria or backache which are typical symptoms of overt hyperparathyroidism, though no hormonal or serum calcium turnover evaluation was available. The number of calcified opacity increased insidiously.

As a matter of course, we considered the possible diagnosis of Sjogren's syndrome as a responsible disorder for calcification besides the

sarcoidosis from the point of having a positive Schirmer test and rose-bengal test. Such a diagnosis, however, did not coincide with the pathological findings obtained from lymphnode biopsy at 1956, 1984 and stomach biopsy and lip biopsy at 1984. It may be plausible to consider rather sarcoid involvement resembling Sjogren's syndrome than Sjogren's syndrome per se⁴⁾. The echogram of thyroid gland may also suggest sarcoid involvement because of no abnormal thyroid hormonal levels and normal technetium scintigram except high titers of thyroid test and microsome test. Slightly elevated liver enzyme, GTP, LAP, AL-P, may also be manifestations of sarcoid process in liver.

Hitherto, calcification in sarcoidosis were frequently noted in mediastinal lymphnodes²⁾, renal region³⁾ and not frequently in brain⁵⁾ and thyroid gland⁶⁾ usually in the case of having more than 10 years of clinical history. The mechanism for calcification deposit has been discussed entirely in speculation in literature; complication with tuberculosis⁷⁾, association with histoplasma infection⁸⁾, immunological abnormality⁸⁾, deranged calcium metabolism⁹⁾ and steroid treatment¹⁰⁾. As to the causes of calcification in our case, there was no evidence of active tuberculosis in her clinical course and furthermore, additional steroid administration for a month after discharge did not worsen her illness. Histoplasmosis is at most rarely noticed in Japan and related symptoms or pathological evidence were not documented in this case. As far as a steroid therapy as a candidate is concerned, calcified process developed before steroid medication so that steroid has no responsibility in formation of calcification. As abovementioned, mechanism of calcification is uncertain in our case, however, we believe that calcification may have some linkage to immunological abnormality because calcified lesions are distributed chiefly to reticuloendothelial organs such as liver, spleen and lymphnodes.

It is reported that calcification in lymphnodes occurs in about 5% of cases of sarcoidosis, usually as a late manifestation of advanced disease stage, having predominantly the form of the classic egg shell calcification¹⁰⁾ and that the lung

parenchymal lesions practically never calcify¹¹⁾. This explanation is not fit with our case in the point of early development of calcification and suspecting involvement of lung parenchymal lesions.

As a very rarely distributed complication, we here presented and discussed an interesting case of sarcoidosis with early developed calcified deposit through a body. We must pay attention to sarcoidosis as a calcifying disorder even if in Japan in which pulmonary tuberculosis is a prevailing and predominant disease as calcification deposits.

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