Familial Sarcoidosis in Taiwan

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Sarcoidosis is a multisystemic granulomatous disease of unknown etiology and is uncommon in Taiwan. No cases of familial sarcoidosis have been reported in Taiwan. In this article, we report a mother and son pair who had sarcoidosis. The 56-year-old mother sought medical help for chronic cough for 3 months in 1993. Enlarged mediastinal lymph nodes were demonstrated on chest computed tomography. Besides, two small erythematous papules on her face were observed. Mediastinoscopic biopsy and skin biopsy showed non-caseating granulomatous inflammation. Sarcoidosis was thus diagnosed. The human leukocyte antigen (HLA)-typing of the patient was HLA-A2, A11, B35, B39, CW4, CW7, DR8 and DQ6. Eleven years later, her son was also diagnosed with sarcoidosis proved by mediastinoscopic biopsy. His HLA-typing was HLA-A2, A24, B39, B48, CW7, CW8, DR8 and DQ6. This is the first report of familial sarcoidosis in Chinese people. More cases are needed for further investigation of genetic predisposition among Chinese people. [J Formos Med Assoc 2007;106(6):499–503]

Key Words: Chinese, familial sarcoidosis, human leukocyte antigen

Sarcoidosis is a multisystemic disorder of unknown cause, characterized by widespread non-caseating granuloma, and commonly affects the young adult. The clinical presentation of the disease is protean. It may involve the chest, skin, eye, liver, spleen and nervous system. Sarcoidosis is uncommon among Chinese people. In Taiwan, the first case was reported in 1960. The incidence rate was only 0.027 per thousand admissions between 1990 and 1995.1 Family history seemed a strong risk factor to induce sarcoidosis, especially in African-Americans.2 Substantial evidence exists for a genetic predisposition to sarcoidosis. However, no cases of familial sarcoidosis have been reported among Chinese people. Herein, we report a familial case of sarcoidosis in Taiwan with human leukocyte antigen (HLA)-typing performed.

Case Reports

Case 1

Mrs Huang, a 56-year-old lady, had experienced dry cough for 3 months and was admitted to hospital in May 1993. She was the president of an elementary school. She was robust in the past. Major systemic disease or cigarette smoking was denied. Physical examination was unremarkable except for two small erythematous papules over the face. Chest radiography showed a nodular shadow near the aortic knob. An anterior mediastinal mass was suspected. Chest computed tomography (CT) with contrast revealed enlarged lymph nodes over bilateral upper and lower paratracheal, right tracheobronchial, aorto-pulmonary window, subcarinal and bilateral intrapulmonary areas (Figure 1). Pulmonary function test (PFT)
disclosed mild restrictive ventilatory impairment (FEV1: 1.38 L, 61%; forced vital capacity [FVC]: 1.85 L, 67% predicated; FEV1/FVC = 74%; total lung capacity: 3.46 L, 80% predicated). Diffusing capacity of carbon monoxide (DLco) showed moderate reduction of gas exchange (DLco: 13 mL/mmHg/min, 54% predicated; DLco/alveolar volume [VA]: 4.26 L/min/mmHg, 83% predicated). No hypercalcemia or hypercalciuria was noted. Bronchoscopy was performed, which showed diffuse capillary engorgement and congestion in left bronchial trees. Additionally, the lumen of the left main bronchus was also narrowed. Bronchoscopic biopsy was performed via the left common basal bronchus. Mediastinoscopic biopsy of left paratracheal lymph nodes and skin biopsy of the facial lesion were also performed. All the pathology results showed chronic non-caseating granulomatous inflammation (Figure 2). Sarcoidosis with mediastinum and skin involvement was impressed. The HLA-typing of the patient was HLA-A2, A11, B35, B39, CW4, CW7, DR8 and DQ6. She was regularly followed up in the outpatient department without steroid use. No progression in clinical symptoms and chest films were observed between 1993 and 2004. (She refused chest CT examination after initial diagnosis due to no further discomfort.)

Case 2

Mr Huang, the son of Mrs Huang, a 43-year-old male, was admitted in February 2004 due to chronic cough. He was a current smoker of one pack per day for 20 years. He was an engineer in the Metro Taipei, but he had never worked in the tunnel. His past medical history was negative for major systemic diseases. Physical examination and laboratory data were unremarkable. Chest radiography revealed bilateral hilar enlargement without infiltration (Figure 3). Chest CT showed multiple lymphadenopathy over the subcarinal, pretracheal and paratracheal regions. PFT showed normal ventilation function. DLco indicated moderate reduction of gas exchange (DLco: 18.5 mL/mmHg/min, 55% predicated;...
DLco/VA: 4.07 L/min/mmHg, 75% predicated). No hypercalcemia was noted. Bronchoscopy was performed with negative findings. Mediastinoscopy was performed, and paratracheal, tracheobronchial and subcarinal lymph nodes were taken for pathologic examination. Pathology results showed chronic non-caseating granulomatous inflammation (Figure 4). Pulmonary sarcoidosis stage I was diagnosed. The HLA-typing of this patient was HLA-A2, A24, B39, B48, CW7, CW8, DR8 and DQ6. He was also followed up in the outpatient department without steroid use. He was lost to follow-up due to immigration to the United States of America.

As previously mentioned, his mother was diagnosed with sarcoidosis 11 years ago. No other family members were diagnosed with sarcoidosis. They did not receive examination of HLA-typing because they did not live in Taiwan.

**Discussion**

Sarcoidosis is a granulomatous disease of unknown etiology, affecting multiple organs. Estimates of the prevalence of sarcoidosis range from less than one case to 40 cases per 100,000 population, with an age-adjusted annual incidence in the United States of 10.9 per 100,000 for whites and 35.3 per 100,000 for blacks.\(^1\) In Taiwan, although the disease-specific rate per thousand admissions increased from 0.004 in the 1980s to 0.027 in the 1990s, sarcoidosis remains an uncommon disease.\(^2\)

Although sarcoidosis can affect multiple organs, the lungs or intrathoracic lymph nodes are involved in more than 90% of patients with the disease.\(^1\) The most common symptoms of pulmonary sarcoidosis are shortness of breath, dry cough and chest discomfort.\(^1\) Radiologic appearance is classified into five stages.\(^1\) Radiographic staging can be utilized as a prognostic factor and act as a guide for treatment.\(^1,3-5\)

Diagnosis of sarcoidosis is based on a compatible clinical picture, histologic evidence of non-caseating granuloma and excluding other known causes contributing to this pathologic response.\(^1\) Biopsy by fiberobronchoscopy is the most frequent procedure used to diagnose pulmonary sarcoidosis.\(^6,7\) Marked increase in the proportion of lymphocytes recovered from bronchoalveolar lavage (BAL) was observed in active pulmonary sarcoidosis. In the majority, BAL lymphocytosis is typified by a dominance of CD4\(^+\) T cells in contrast to the CD8\(^+\) BAL lymphocytosis seen in patients with hypersensitivity pneumonitis, viral infection, and many drug reactions.\(^8,9\) Mediastinoscopy is considered for cases in which lymphoma or other intrathoracic malignancy cannot be reasonably excluded.\(^1\)

Observation is suggested in asymptomatic patients or those with mild disease.\(^1,10\) Spontaneous remission or disease stabilization is reported to occur in approximately two thirds of cases.\(^1\) In general, oral corticosteroids are indicated as the first-line treatment for severe ocular, neurologic, or cardiac sarcoidosis, malignant hypercalcemia, symptomatic or progressive stage II pulmonary disease (as reflected by serial pulmonary function decline) and stage III pulmonary disease.\(^10\)

Several factors are thought to be related to the disease, such as environment, gene and immunology.\(^1\) Genetic factors may play a part in the predisposition to sarcoidosis.\(^10\) At present, race and family history of disease are the most strongly identified risk factors to developing sarcoidosis, thus supporting the notion that there is a genetic
susceptibility to the development of this disease. Familial aggregation and racial difference in disease incidence have been reported worldwide, ranging from 4.3% (Japan), 4.7% (Finland), 5.9% (UK), to 17% (African-Americans). In the United States, African-Americans are at least four times more likely to develop the disease than are white Americans. Within the same family, sibling pairs are most common and mother–daughter pairs are more frequent than father–son pairs. Monozygotic twins appear more likely to have sarcoidosis than dizygotic twins, strongly suggesting a genetic component to the disease. It is likely that the genetic susceptibility to sarcoidosis involves several genes. Siblings had the highest relative risk, followed by avuncular relationships, grandparents and then parents. Genetics may be important not only in defining the risk of disease, but also in determining the pattern of disease, its severity and prognosis.

Candidate gene associations with sarcoidosis risk remain unconfirmed. These genes may be involved in T cell function, regulation of antigen recognition and processing, or the regulation of matrix deposition that favors granuloma formation and progressive fibrosis. The major histocompatibility complex (MHC) region, on chromosome 6p, was an important target of investigation. Association studies and linkage analysis support the idea that candidate disease susceptibility gene(s) of the human genome is located on the short arm of chromosome 6. This is also the locus of the MHC, which is a critical part of the human immune system. Studies have suggested that genes encoding the HLA portion of the MHC play an important role in determining the risk and clinical course of sarcoidosis. They pointed out that B8 and CW7 antigens prevail in patients suffering from the disease as compared with a control group of healthy people. In another study, which recruited patients with pulmonary sarcoidosis in northern Poland, antigens HLA-B8 and CW7 are significantly more frequent as compared with the control group of healthy people. Besides the HLA genes conferring susceptibility, they may also be involved in disease outcomes. In addition, polymorphisms in genes of the interleukin-1 family, vitamin D receptor and the promoter region of the gene for tumor necrosis factor-α have been reported to be associated with the pathogenesis of sarcoidosis. One study that genotyped 122 affected siblings from 55 families in Germany showed significant excess of marker haplotype sharing among affected siblings, especially at marker locus D6S 1666 in the class III gene cluster. Genotyping for HLA-DQB1 has also been studied in familial sarcoidosis. Over-representation of DQB1*0603 and DQB1*0604 among alleles shared by affected first degree relatives was concluded.

After a thorough search of the literature via MEDLINE and PubMed, we found that no cases of familial sarcoidosis have been reported among Chinese people. This is the first report of familial sarcoidosis among Chinese people, with HLA-typing performed. In the two cases we reported, they had some HLA loci in common, such as A2, B39, CW7, DR8 and DQ6. If genetic factors predisposing to sarcoidosis do exist, they may reside in these loci. This assumption may be arbitrary because the mother and her son may share the common HLA in part. However, HLA-CW7 has also been reported to be a frequent HLA locus in English and Polish people with sarcoidosis. It seems reasonable that the same linkage may be present in Chinese people. Nevertheless, more cases are needed for further investigation of genetic predisposition.

References

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