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Clinicopathologic features of sporadic inclusion body myositis in China

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ABSTRACT

This study is to investigate the clinical and pathologic features of sporadic inclusion body myositis (sIBM) in China. We retrospectively evaluated the clinical and pathological features of consecutive patients in our department between January 1986 to May 2012. Total 28 cases of sIBM (20 males, 8 females, mean age was 56.93 ± 8.79) were obtained by review of all 4099 muscle biopsy reports. The proportion of sIBM was 0.68% (28/4099) in China. Muscle weakness of quadriceps appeared 100% in 28 cases, while conspicuous atrophy of quadriceps appeared only in five cases (17.86%). Creatase values of 28 patients with sIBM were normal or mildly elevated. Muscle biopsies showed that atrophic fibers resembled more frequent in small angular and irregular shape (82.14%), less common in small round shape (17.86%). Rimmed vacuoles resembled crack (67.86%) and round (32.14%) shape. Mononuclear cell invasion into necrotic muscle fibers (35.71%) was more frequent than non-necrotic muscle fibers (7.14%). sIBM was still a rare disease in China compared to other countries. There were some certain specific pathological characteristics existed in Chinese sIBM patients.

1. Introduction

Sporadic inclusion body myositis (sIBM), a progressive inflammatory skeletal muscle disease, occurs mainly in over 60-year-old patients [1]. The clinical and pathological features of sIBM were available in many countries, but did not reported in China. Since technique of enzyme-histochemistry method in muscle biopsy was not popularly for myopathy, few sIBM cases were studied and reported in China [2]. Meanwhile, there was also rare epidemiological data of sIBM in the world. The prevalence rate was reported differently among different countries and ethnic groups [3]. And the epidemiological data of sIBM in China was not available yet.

To study the clinical and pathological features of sIBM in China, we investigated the clinical manifestations, serological examination, electrophysiology, and muscle pathology in 28 sIBM cases. In addition, we surveyed all suspected myopathy patients who were subjected to muscle biopsy in our department. And we calculated an indirect epidemiological prevalence rate of sIBM in China.

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2. Patients and methods

2.1. Patients

From January 1986 to May 2012, a total of 4099 patients with suspected myopathy around China were subjected to muscle biopsies in the neuropathology laboratory of our hospital. 28 patients were diagnosed as sIBM. All their medical records, electromyography (EMG) reports and muscle histopathology were collected. The muscle biopsies sites in this study were quadriceps and/or biceps. All 28 patients did not have dysphagia. The diagnose depended on 2011 European Neuromuscular Centre diagnostic criteria for inclusion body myositis [4].

2.2. Data collection

Study protocol data included: (1) detailed general history: gender, age at onset, initial symptom or sign, clinical course, family history; (2) muscle power: manual muscle testing (extremities, facial muscles, oculorotatory muscles), pharyngeal portion muscles, distribution and degree of muscle weakness and atrophy, progression pattern; (3) laboratory data: serum creatine kinase, nerve conduction velocity, muscle biopsy and other examination.

2.3. Histopathologic study

Muscle samples were frozen in liquid nitrogen immediately after removal and stored at −80 °C. Transverse serial frozen muscle sections were stained with hematoxylin and eosin (H&E), periodic acid-Schiff (PAS), oil red O (ORO), Gomori trichrome stain, nicotinamide adenine dinucleotide dehydrogenase (NADH), nonspecific esterase (NSE) and adenosine triphosphatase (ATPase) staining after incubation in pH 4.3, 4.5 and 10.6. Morphometric evaluation of muscle specimens was performed by light microscopy. Ultrathin sections were prepared in epon-embedded material, stained with osmic acid and examined by an electron microscope.

2.4. Statistical analysis

Dichotomous variables were analyzed by chi-square test; continuous variables were presented as mean ± SD and analyzed by Mann–Whitney *U*-test. All statistical tests were two-tailed. $P < 0.05$ was considered as statistically significant. In this study, all statistical analysis was performed by SPSS13.0 statistical software.

3. Results

3.1. Prevalence and onset age

We analyzed 28 patients with sIBM in our department from January 1986 to May 2012. The results showed that the proportion of sIBM was 0.68% (28/4099) in this group.

Among all 28 patients with sIBM, there were 20 male patients (71.43%) and 8 female patients (28.57%). The onset age ranged from 38 to 71 years (51.5 ± 7.3 years). The diagnosis age ranged from 41 to 78 years (56.93 ± 8.79 years). In detail, three patients were 40–49 years old (10.71%), 16 patients were 50–59 years old (57.14%), 6 patients were 60–69 years old (21.43%), and 3 patients were older than 70 (10.71%). And the time course from onset to diagnosis ranged from 1.5 to 14 years (5.54 ± 3.15 years), which was 5.15 ± 3.56 years for men and 6.5 ± 1.51 years for women, respectively.

3.2. Clinical features

The clinical course of 28 patients with sIBM was chronic and progressive. As for the onset symptom of total 28 patients with sIBM, 17 cases presented both lower limbs weakness (60.71%), 5 cases for both upper limbs (17.86%) and 6 cases for four limbs weakness (21.43%). More clinical details were listed in Table 1.

3.3. Laboratory examination

Serum creatase of 28 patients with sIBM were normal or mildly elevated. The mean serum CK value of 28 patients with sIBM was 397.38 ± 295.06 (79–1384) u/L. The mean serum LDH value of 28 patients with sIBM was 218.21 ± 64.32 (120–374) u/L. The mean serum ALT and AST value was 30.21 ± 18.41 (12–97) u/L and 27.67 ± 13.85 (11–56) u/L, respectively.

The sIBM patients' creatase values between different disease duration groups were listed as supplemental data. CK values of patients with sIBM for less than 5 years duration were significantly higher than that of more than 5 years duration (544.82 ± 376.34 vs. 272.62 ± 109.78) u/L ($P < 0.05$). Also, ALT values were higher in patients with <5 years duration than that in patients with ≥5 years duration (38.82 ± 21.79 vs. 22.92 ± 11.32) u/L ($P < 0.05$).

EMG reports showed that there were 21 cases with myogenic lesion, while seven cases with both myogenic lesion and neurogenic lesion.

3.4. Myopathological features

Pathological features of patients with sIBM were summarized in Table 2. Atrophic fibers presented small angularity or irregularity (82.14%, 23/28) (Fig. 1A) and small round shape (17.86%, 5/28) (Fig. 1B). Rimmed vacuoles resembled crack (Fig. 2A) (67.86%, 19/28) or round (Fig. 1C) (32.14%, 9/28).

Table 1 – Clinical symptom of 28 patients with sIBM.

Clinical manifestation	Cases	Percentage (%)
Onset symptom		
Upper limbs weakness	5	17.86
Lower limbs weakness	17	60.71
Four limbs weakness	6	21.43
Clinical symptoms		
Facial muscle weakness	2	7.14
Dysphagia	2	7.14
Neck muscle weakness	9	32.14
Proximal upper limb weakness	22	78.57
Distal upper limb weakness	23	82.14
Proximal lower limb weakness	28	100
Distal lower limb weakness	20	71.43
Quadriceps atrophy	5	17.86

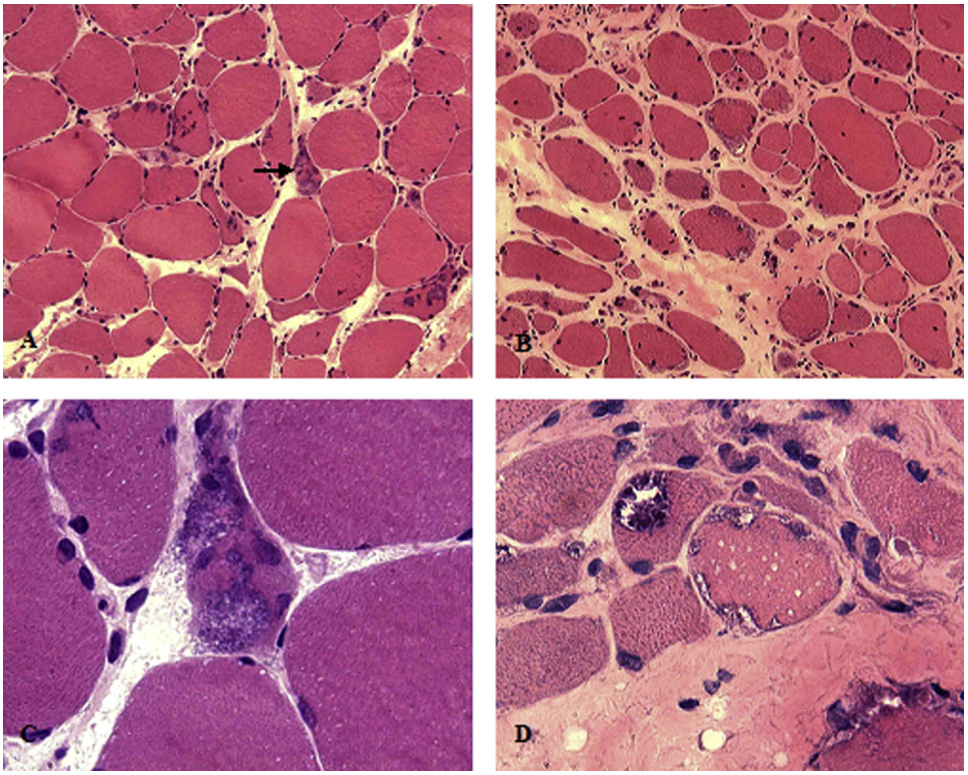

Fig. 1 – Morphous of rimmed vacuoles and inclusion bodies showed as below. (A) Many atrophic fibers showed as small-angular (arrow), in which there were some rimmed vacuoles (hematoxylin & eosin, original magnification ×100). (B) In this cross-section of muscle, many atrophic fibers showed as small-small-rounded, in which there were some rimmed vacuoles, with some internal nuclei within fiber, disintegration and hypertrophy of fibers (hematoxylin & eosin, original magnification ×100). (C) This was a magnification of (A). Many fine particle-like inclusion bodies located in round rimmed vacuoles in fiber (hematoxylin & eosin, original magnification ×200). (D) Many coarse particle-like inclusion bodies were seen in round rimmed vacuole of fiber, while other fine particle-like inclusion bodies were seen in crack rimmed vacuoles (hematoxylin & eosin, original magnification ×400).

Inclusion body appeared fine granules as sand-like particles (Figs. 1C and 2D) (78.57%, 22/28) and coarse granules (21.43%, 6/28) (Fig. 1D). Only two cases (7.14%) presented mononuclear cell invasion in non-necrotic muscle fibers (Fig. 2B), while 10 cases presented mononuclear cell invasion in necrotic muscle fibers (35.71%) (Fig. 2A). Inflammatory cell infiltration was observed (Fig. 2C) in 15 cases (53.57%), but not observed in the other 13 cases (46.43%). Moreover, infiltration of inflammatory cells in the walls of perimysial venules and arterioles (Fig. 2D) was observed in nine cases (32.14%). For Gomori trichrome staining, RRF (Fig. 3A) was observed in three patients' muscle samples (10.71%) while red staining inclusion bodies (Fig. 3B) were showed in all samples. Excess lipid droplets in three cases presented positive for ORO staining (10.71%). ATPase staining showed an equal distribution of muscle fiber types in 24 cases (85.71%). However, type I fiber was observed dominantly in only three cases (10.71%), and type II fiber presented dominantly in only one case (3.57%).

4. Discussion

Sporadic inclusion body myositis is a distinct progressive inflammatory skeletal muscle disease. Its cause and effective treatment still remains unknown [5]. It usually occurs in over 50-year-old patients. In 1967, Chou [6] first described the specific pathological manifestation of inclusion body and rimmed vacuoles. In 1971, Yunis and Smamha [7] first introduced the concept of inclusion body myositis. It was verified later by Carpenter et al. [8] and reported clinical feature in progressive course and finger flexor, wrist flexor and knee flexors.

The epidemiological data of sIBM was reported distinctively among different countries and ethnic groups. The prevalence rate was reported to be 4.9 per million in the Netherlands [9], 9.3 per million in Western Australia (WA) [10] and 10.7 per million in Connecticut, USA [11]. Because muscle biopsy was not popularly in suspected myopathy patients, there were only few case reports of sIBM published, and no epidemiological data was reported in China. In our study, we investigated total 4099 patients with possible neuromuscular disorders all over the country from January 1986 to May 2012. All patients were examined by muscle biopsy. And among these 4099 cases, total 28 cases of sIBM patients were analyzed and the proportion of sIBM cases was calculated to be 0.68%. Since the patients were from the whole country, it represented indirect epidemiological data of sIBM in China.

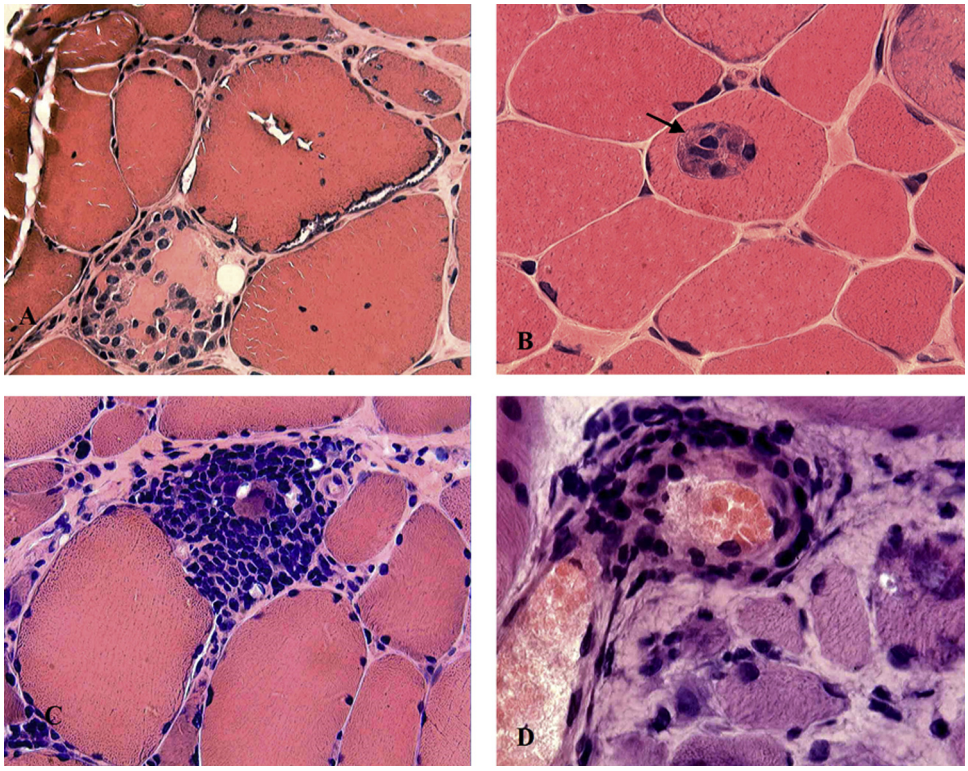

Fig. 2 – Infiltration of inflammatory cells showed as below. (A) Many fine particle-like inclusion bodies adhered to wall of crack rimmed vacuole in fiber. Mononuclear cell invasion of necrotic muscle fibers could be seen (hematoxylin & eosin, original magnification ×200). (B) Mononuclear cell invasion (arrow) of non-necrotic muscle fibers (hematoxylin & eosin, original magnification ×400). (C) Many inflammatory cells infiltrated gaps between fibers (hematoxylin & eosin, original magnification ×200). (D) Infiltration of inflammatory cells in the walls of perimysial vessel (hematoxylin & eosin, original magnification × 200).

As reported by Badrising [12], it was most frequent in the quadriceps and less common in the finger flexors and pharyngeal muscles. And quadriceps weakness tended to occur more frequently in men. Our study partly affirmed these results in Chinese patients. Among 28 sIBM patients, 20 cases were male and 8 cases for female. The male-to-female ratio was 2.5:1. Onset symptom showed most frequent in the quadriceps and less common in the forearm muscles, but no case in the pharyngeal muscles.

Quadriceps occurred most frequently as others reported. But in this study, although lower limbs weakness proportion was 100% in 28 sIBM patients, only five cases showed obvious quadriceps atrophy (17.86%), which was slightly different from other countries.

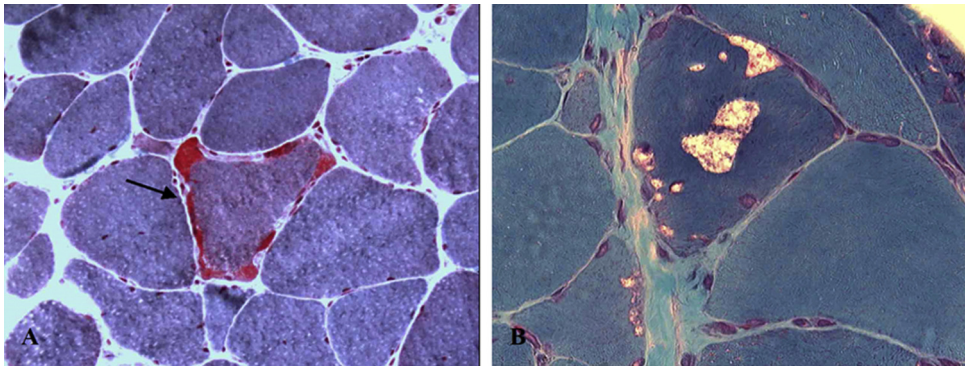

Fig. 3 – Gomori trichrome staining of muscle histopathology in patients with sIBM demonstrating (A) RRF was showed (arrow) (original magnification ×200) and (B) inclusion bodies of some rimmed vacuoles in fibers were stained as red (original magnification ×200). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of the article.)

Table 2 – Pathological features of 28 sIBM patients.

	Cases	Percentage (%)
Morphous of atrophic muscle fiber		
Small angular	9	32.14
Small round	5	17.86
Irregular	14	50.00
Internal nuclei within fiber	12	42.86
Muscle fiber hypertrophy and split	18	64.29
Morphous of rimmed vacuoles		
Crack	19	67.86
Round	9	32.14
Rimmed vacuoles protrude	2	7.14
Morphous of inclusion body		
Fine particles	22	78.57
Coarse particles	6	21.43
Mononuclear cell invasion of non-necrotic muscle fiber	2	7.14
Mononuclear cell invasion of necrotic muscle fiber	10	35.71
Inflammatory cell infiltration	15	53.57
No inflammatory cell infiltration	13	46.43
Peri-vascular inflammatory infiltration	9	32.14
No peri-vascular inflammatory infiltration	19	67.86
RRF	3	10.71
Red staining inclusion body in Gomori trichrome stain	28	100
Excess lipid droplets on ORO staining	3	10.71
No excess lipid droplets on ORO staining	25	89.29
Equal distribution of muscle fiber type	24	85.71
Type I fiber dominantly	3	10.71
Type II fiber dominantly	1	3.57

sIBM develops gradually progressively. With the aggravation of symptoms, neck and bulbar muscles involvements are gradually observed, which generally indicates that it significantly deteriorated. Without control, it will finally lead to respiratory difficulties and even death. Therefore, the probability estimation of the muscles involvements mentioned above is meaningful to diagnose. Lynn et al. [13] reported that bulbar muscle was more probably to be involved in sIBMs than in other inflammatory myopathies. Felice and his colleagues [11] reported that 38–84% sIBM patients suffered from bulbar muscle. Moreover, bulbar muscle involvement was more frequent in male patients in a study on 26 cases of sIBM patients with bulbar muscular disorders [14]. Our study suggested that only two of the total 28 sIBM cases (7.14%) involved bulbar muscular, which was different from the results of the former studies.

Serum creatase values were normal or slightly increased in these sIBM patients. CK and ALT values were higher in patients with <5 years duration than that in patients with ≥5 years duration, indicating that creatase increased significantly in the early cause of sIBM but tended to decrease with the development of disease. The possible reason was that the muscle involvements deteriorated and further led to the muscular atrophy and the reduction of creatase.

The pathological features of sIBM are commonly described as follows: myofiber necrosis and regeneration; endomysial mononuclear cell infiltration; invasion of non-necrotic fibers by mononuclear cells; vacuolated muscle fibers (rimmed vacuoles); ubiquitin-positive inclusions and amyloid deposits in muscle fibers; nuclear and/or cytoplasmic 16–20 nm filamentous inclusions under electron microscopy [15]. By contrast, the Chinese sIBM patients in our study followed most of the regular pathological features. A specific pathological feature was that mononuclear cell infiltrated more frequent in necrotic muscle fibers than in non-necrotic muscle fibers. This might be a special characteristic of Chinese sIBM patients. Also, we found that rimmed vacuoles resembled crack or round and inclusion body mostly looked like fine sand-like granules.

5. Conclusions

In conclusion, the proportion of sIBM in all neuromuscular disorders was 0.68% in China. The onset symptom of sIBM in this study was mainly weakness in both lower limbs. Clinical manifestation mostly showed proximal lower limbs and distal upper limbs weakness. However, only 17.86% cases were quadriceps atrophy. Creatase value was normal or mildly elevated, which was mostly notable in early stage of disease and not significant in later stage. The pathological features of sIBM followed as below: The atrophic muscle fibers were mostly presented small angle or irregularity. The rimmed vacuoles mostly resembled crack and the inclusion body appeared fine granules as sand-like particles. There were rare mononuclear infiltrations in non-necrotic muscle fiber, while more in necrotic muscle fibers. Half of the cases showed inflammatory cell infiltration, and one third of the cases showed peri-vascular infiltration in inflammatory cells. The study provided the evidence for the specific clinical and pathological characteristics of sIBM in China and a foundation for the diagnosis and further research.

Conflict of interest

None declared.

Acknowledgment and financial support

None declared.

Ethics

The work described in this article has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans; Uniform Requirements for manuscripts submitted to Biomedical journals.

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