RHEUMATOLOGY

Rheumatology 2010;49:1354–1360
doi:10.1093/rheumatology/keq073
Advance Access publication 12 April 2010

Original article

Increased ferritin predicts development and severity of acute interstitial lung disease as a complication of dermatomyositis

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Abstract

Objectives. Acute/subacute interstitial pneumonia (A/SIP) is an intractable and fatal complication of DM. Since a useful indicator predicting the complication of A/SIP has not been found, the aim of this study was to determine whether serum ferritin is a potential predictive indicator of the occurrence of A/SIP in 64 patients with DM.

Methods. Of the total patients enrolled, 19 had A/SIP, 24 had chronic interstitial pneumonia and 21 were without interstitial lung disease (ILD). Clinical manifestations and laboratory data were obtained from medical records on admission.

Results. Serum ferritin levels were extremely high in patients with DM with A/SIP. It was significantly higher in DM with A/SIP than that in DM without A/SIP (median 790 *vs* 186 ng/ml; $P < 0.0001$). The cumulative survival rate for 6 months was 62.7% in patients with DM with A/SIP. Moreover, the cumulative survival rate was significantly ($P = 0.016$) lower in the group with ferritin levels $\geqslant 1500$ ng/ml than the rate in the group with ferritin levels <1500 ng/ml.

Conclusions. Serum ferritin can be useful as a predictor of the occurrence of A/SIP and correlates with the prognosis of A/SIP in DM. The intensive treatment using combination therapy with various immunosuppressant agents should be chosen for patients with ILD with DM showing hyperferritinaemia, especially levels >1500 ng/ml.

Key words: Dermatomyositis, Interstitial lung disease, Ferritin, Macrophage activation.

CLINICAL SCIENCE

Introduction

DM is characterized by the inflammation of skin and muscle [1], occasionally complicated with interstitial lung disease (ILD), which is classified into two subsets, acute/subacute interstitial pneumonia (A/SIP) and chronic interstitial pneumonia (CIP) [2–6]. A/SIP is of prime importance in the clinical management of patients with DM because it is an intractable and a life-threatening complication [4, 6–8]. Clinically amyopathic DM (C-ADM) has typical skin lesions with amyopathy or hypomyopathy for >6 months [9] and was recently reported to be complicated with A/SIP [6, 10, 11]. Even though intensive combination therapy, including corticosteroid and immunosuppressive agents, was provided immediately after diagnosis, most of the patients with A/SIP in C-ADM did not respond [6, 11]. Eventually, C-ADM with A/SIP showed a rapidly progressive pattern with a 6-month survival rate of 40.8% [11]. Although C-ADM may be a useful indicator for the occurrence of A/SIP retrospectively, ILD with C-ADM does not always develop as a feature of A/SIP. It is possible that two different subsets of ILD with C-ADM may be A/SIP and CIP [12]. Fathi *et al.* [13] reported that patients with myositis with ILD needed careful evaluation of clinical features as well as pulmonary function tests and

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Submitted 17 September 2009; revised version accepted 16 February 2010.

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radiologic features during follow-up because the course of ILD could not be predicted on the first examination. Taken together, it is imperative to establish a novel strategy for the diagnosis of early-stage A/SIP as a complication of DM.

Ferritin is the major molecule for iron storage and has a crucial role in the sequestration of potentially harmful molecules of reactive iron [14, 15]. Ferritin is located in the cytoplasm, mitochondria, nuclei and serum [14]. Ferritin can be secreted by the liver, T lymphocytes and macrophages. Very high serum levels of ferritin have been reported in systemic-onset juvenile idiopathic arthritis, adult-onset Still's disease and haemophagocytic syndrome (HPS) related to CTDs, which is within the spectrum of secondary haemophagocytic lymphohistiocytosis (HLH) [16–19]. Macrophage activation syndrome (MAS) is now considered as a special term to refer to a form of secondary HLH seen in the context of rheumatic disorders [16, 19]. The pathophysiology of MAS involves lack of regulation of T lymphocytes and excessive production of cytokines [16]. High levels of serum ferritin may reflect the aberrant production of ferritin by activating macrophages.

We have seen several patients in whom the serum ferritin level was extremely high and correlated with the activity of A/SIP, not dermatitis and myositis. These cases were more refractory to the conventional treatment and were more life threatening than those with CIP.

Taken together, we considered that serum ferritin may be an important marker not only in an acute-phase reaction, but also associated with the pathophysiology in A/SIP with DM, different from CIP with DM. In the present study, we explored the association of serum ferritin levels with the development of A/SIP in patients with DM. Further studies estimated a predictive value of the serum ferritin concentration for the mortality of patients with DM with A/SIP.

Materials and methods

Patients

This retrospective study included patients admitted to our hospital from 1 August 1992 to 31 January 2009. All the enrolled patients suffered from skin rash, myopathy or respiratory symptoms (or a combination thereof) on admission. They were diagnosed as having DM based on the criteria of Bohan and Peter [20]. Patients with overlap syndrome such as SLE and SSc were excluded. Although a few patients had received a low- or an intermediate-dose corticosteroid before admission, corticosteroid or immunosuppressive agents were not given to most patients on admission. Clinical data were obtained from medical records on admission. The study was approved by the ethical committee in our institution (an ethics committee of Institute of Rheumatology, Tokyo Women's Medical University), according to the Declaration of Helsinki. Muscle weakness was evaluated by manual muscle testing. The normal ranges of serum ferritin are 18.6–261 ng/ml for men and 4.0–64.2 ng/ml for women. Other blood tests included liver enzymes [alanine aminotransferase (ALT), aspartate aminotransferase (AST) and γ-glutamyl transpeptidase (γ-GTP)], creatine kinase (CK), lactate dehydrogenase (LD), CRP, ANA and anti-Jo-1 antibody, measured by the standard methods.

Classification of ILD

ILD was assessed by chest radiography and CT or high-resolution CT of the chest. ILD with DM was divided into two forms: A/SIP and CIP. A/SIP is defined as a rapidly progressive ILD within 3 months from the onset of symptoms. CIP is defined as an asymptomatic non-rapidly progressive ILD or slowly progressive ILD over 3 months, referring to the International Consensus Statement of Idiopathic Pulmonary Fibrosis of the American Thoracic Society and the European Respiratory Society [21]. The designation of A/SIP *vs* CIP was made blindly without knowledge of the laboratory results, including serum ferritin tests.

Statistical analysis

Statistical analyses were performed using the Fisher's exact test for the comparison of frequencies and the Mann–Whitney U-test for comparisons of median values. The data were analysed using JMP software. Receiver operating characteristic (ROC) analyses were performed for a mathematical expression of different serum ferritin concentrations as cut-off points. The cumulative survival rate was calculated using the Kaplan–Meier test. The log-rank test was also used to compare survival. $P < 0.05$ was considered to indicate statistical significance.

Results

Comparison of clinical manifestations between DM patients with and without A/SIP

As shown in Table 1, 64 patients with DM were enrolled in this study, including 19 with A/SIP, 24 with CIP and 21 without ILD. Table 1 shows the results of the first examinations on admission. The age at onset was 45.8 (14.5) years [mean (S.D.)] in DM with A/SIP, with no significant difference among all the subsets. The median value of the duration between the onset of myositis or dermatitis and hospitalization was 2 months in patients with DM with A/SIP, which was significantly shorter than those without A/SIP. Fourteen patients (72.2%) with DM with A/SIP reported muscle weakness. Although the value of CK and CK to LD ratio showed no significant difference among all the subsets, AST, ALT and γ-GTP concentrations were significantly higher in patients with DM with A/SIP than those with DM without A/SIP. Although elevation of liver enzymes can be attributed to muscle enzymes, they can also be attributed to liver injury because CK and the CK to LD ratio were lower and the γ-GTP concentration was higher in patients with A/SIP with DM. The CRP level showed no significant difference between patients with DM with A/SIP and those with DM with CIP. The frequency of Jo-1 positivity was significantly lower in patients with DM with A/SIP compared with the frequency in those with DM with CIP.

Table 1 Clinical profiles at the first examinations on admission

Variables	DM with A/SIP	DM with CIP	DM without ILD
No.	19	24	21
Age, years	45.8 (14.5)	48.4 (15.0)	48.4 (14.1)
Female, *n* (%)	16 (84.2)	20 (83.3)	14 (66.7)
Duration, months	2 (1–5)	5 (1–65)***	8 (1–252)***
Muscle weakness, *n* (%)	14 (72.2)	19 (79.2)	16 (76.2)
CK, IU/l	259 (35–4572)	358.5 (42–7641)	496 (61–12 700)
LD, IU/l	555 (243–1122)	528 (187–1030)	425 (192–2975)
CK/LD	0.48 (0.096–4.75)	1.03 (0.10–8.38)	0.77 (0.12–7.06)
AST, IU/l	116 (35–652)	56.5 (19–242)**	43 (19–698)**
ALT, IU/l	90 (30–542)	51 (13–321)**	30 (14–402)***
γ-GTP, IU/l	66 (8–403)	15 (7–148)**	16 (10–72)**
Ferritin, ng/ml	790 (121–8330)	188 (33.1–673)***	160 (4.3–1100)***
CRP, mg/dl	0.9 (0.02–7.66)	0.38 (0–9.3)	0.2 (0–3.2)*
ANA ⩾ 160×, *n* (%)	2 (10.5)	7 (29.2)	6 (28.6)
Jo-1, *n* (%)	0 (0)	5 (20.8)*	0 (0)

The values of age indicate mean (S.D.) and those of duration, CK, LD, CK/LD, AST, ALT, γ-GTP, ferritin and CRP indicate median (range). *$P < 0.05$; **$P < 0.01$; ***$P < 0.001$ compared with DM with A/SIP using Mann–Whitney U-test or the Fisher's exact test.

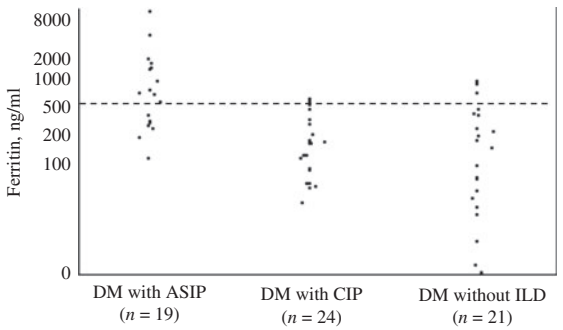
Serum ferritin in patients with DM

The levels of serum ferritin are shown in Table 1 and Fig. 1. Serum ferritin was significantly higher in patients with DM with A/SIP (median, 790 ng/ml; range, 121–8300 ng/ml) than in those with DM without A/SIP. Table 2 shows the comparisons of serum ferritin levels among several patients with DM with A/SIP and without A/SIP. Serum ferritin showed the highest concentration in DM with A/SIP among all subsets of patients with DM ($P < 0.0001$ *vs* DM with CIP, $P = 0.0002$ *vs* DM without ILD, $P < 0.0001$ *vs* DM without A/SIP). The criterion of a high concentration of serum ferritin in 2004 diagnostic guidelines for HLH is a value ⩾500 ng/ml [20]. We evaluated the association of patients with a high concentration of serum ferritin with the complication of A/SIP. As shown in Table 3, high levels of serum ferritin (⩾500 ng/ml) were seen in 63% of patients with DM and A/SIP. As a result of the comparison in the occurrence of A/SIP between the group with <500 ng/ml serum ferritin and the group with >500 ng/ml in patients with DM, the frequency of the complication with A/SIP was significantly ($P = 0.0009$) higher in the group showing levels of serum ferritin ⩾500 ng/ml [odds ratio (OR) 6.9; 95% CI 2.1, 22.4]. Although DM-associated cardiomyopathy was revealed in three patients with ferritin levels ⩾500 ng/ml in the DM subsets without A/SIP, clinical features did not seem to differ between the patients with and without ferritin levels ⩾500 ng/ml in the DM subsets without A/SIP.

Treatment

Table 4 lists the treatments. The frequency of treatment with prednisolone alone was fairly low in patients with DM with A/SIP, whereas the frequency of treatment with immunosuppressive agents was significantly higher in patients with DM with A/SIP than in those with DM without ILD ($P = 0.0016$). Immunosuppressive agents used in patients with DM with A/SIP were CSA for seven patients, intravenous cyclophosphamide therapy (IVCY) for five patients and the combination therapy with CSA or tacrolimus (TAC) plus IVCY for four patients.

Fig. 1 The value of serum ferritin in each group. Dotted line indicates that the value of serum ferritin was 500 ng/ml.



Survival

The cumulative survival rates for 6 months were 62.7 and 100% in patients with DM with A/SIP ($n = 19$) and DM without A/SIP (DM with CIP, $n = 24$; DM without ILD, $n = 21$), respectively (Fig. 2A). The cumulative survival rate for 6 months was significantly different in each group (log-rank test, $P < 0.0001$). Similar to the previous reports, the survival rate was low in DM with A/SIP compared with the other subsets of DM and further analysis was performed in patients with DM with A/SIP.

To define the optimal cut-off point with the highest diagnostic accuracy, we performed ROC for distinct serum ferritin concentrations. The highest area under the curves was calculated for a baseline serum ferritin

concentration of 1500 ng/ml. The two subsets were classified by the serum ferritin concentration of 1500 ng/ml. The cumulative survival rates for 6 months were 28.6 and 82.5% in the group with ferritin levels $\geqslant$1500 ng/ml and the group with ferritin levels $<$1500 ng/ml in DM with A/SIP, respectively (Fig. 2B). The cumulative survival rate was significantly ($P = 0.016$) lower in the group with ferritin levels $\geqslant$1500 ng/ml than that with ferritin levels $<$1500 ng/ml.

Discussion

We have demonstrated for the first time that DM complicated with A/SIP is accompanied with strikingly high levels of serum ferritin. Marie *et al*. [22] described that high serum AST and ferritin levels, the presence of anti-Jo-1 antibody and characteristic microangiopathy may have predictive value for pulmonary dysfunction in patients with PM/DM. Their study included eight patients with CIP among all nine patients (six with PM and three with DM) with ILD. Additionally, previous reports have described that the increase of ESR, CRP, fibrinogen and ferritin could be the potential acute-phase reactants in patients with PM/DM [22, 23]. In the present study, however, serum ferritin levels did not differ significantly between DM with CIP and DM without ILD. Although there was a significant difference in the levels of serum ferritin between DM with A/SIP and DM with CIP, we found no significant difference in the levels of CRP in these two subsets. These findings suggest that the increase in serum ferritin concentration not only reflects acute-phase reactant but is also associated with the pathophysiology of A/SIP observed in patients with DM.

Serum ferritin is an important laboratory hallmark in MAS/HLH [19]. Patients with DM with A/SIP in the present study did not have the complication of HLH and showed significantly higher levels of serum ferritin than did patients with DM without A/SIP. Most patients with CIP observed in DM appeared to be well controlled by corticosteroids and immunosuppressant agents [24–26]; in contrast, patients with A/SIP observed in DM were resistant to a variety of treatments, including corticosteroids, cyclophosphamide, CSA and TAC [6–8, 11]. This distinction in response to treatments might be responsible for cellular phenotypes affecting the pathogenesis of ILD. Alveolar macrophages, which are activated by some antigens, microbes or autoimmune stimuli, are induced to produce leucotriene B4 and IL-8. These mediators stimulate neutrophils to induce the fibrosis process in the lung [27]. In this study, we found an elevation of γ-GTP in A/SIP with DM among all subjects. The elevation of liver enzyme and hyperferritinaemia observed in A/SIP in the present study suggests that macrophages such as Kupffer cells and alveolar macrophages are activated intensively and cause injury to the liver and lungs in DM, although we did not obtain direct evidence of macrophage activation. Whether alveolar macrophages are activated must be investigated using brochoalveolar lavage or lung biopsy in DM with A/SIP.

Inflammatory myopathy with abundant macrophages (IMAM) is characterized by clinical features of DM-like disease and HLH [28]. In IMAM, macrophage infiltration was diffused and correlated positively with both T-cell infiltration and acute muscle fibre damage. However, whether or not the activated macrophages infiltrate to the lung has not been discussed in the case of IMAM. On the other hand, a few reports of DM with HLH have been published recently [29, 30]. Whether macrophages of the lung can activate abnormally in DM with HPS is, as yet, unknown. Those reports suggested that the pathogenesis of DM may be involved in activated macrophages, and these phenomena may determine a critical difference between DM and PM because activated macrophages have not appeared in any subsets of PM. In general, DM is considered to be $CD4^+$ T-cell- and B-cell-mediated muscle inflammation. The complement system is activated, resulting in the deposition on the membrane of an attack complex within capillaries of muscle [31]. On the other hand, autoreactive cytotoxic T cells may mediate MHC I-restricted cytotoxicity against autoantigens expressed

Table 2 Comparison of serum ferritin between the patients with or without A/SIP in DM

Patients	Median (range), ng/ml	*P*-value *vs* DM with A/SIP
DM ($n = 64$)	269 (4.3–8330)	–
DM with A/SIP ($n = 19$)	790 (121–8330)	–
DM with CIP ($n = 24$)	188 (33.1–673)	$<$0.0001
DM without ILD ($n = 21$)	160 (4.3–1100)	0.0002
DM without A/SIP ($n = 45$)	186 (4.3–1100)	$<$0.0001

The *P*-value was estimated by Mann–Whitney U-test.

Table 3 Predictive value of serum ferritin

Patients	Ferritin $<$500 ng/ml	Ferritin $\geqslant$500 ng/ml	*P*-value *vs* DM with A/SIP	OR (95% CI)
DM with A/SIP ($n = 19$), *n* (%)	7 (37)	12 (63)	–	–
DM without A/SIP ($n = 45$), *n* (%)	36 (80)	9 (20)	0.0009	6.9 (2.1, 22.4)

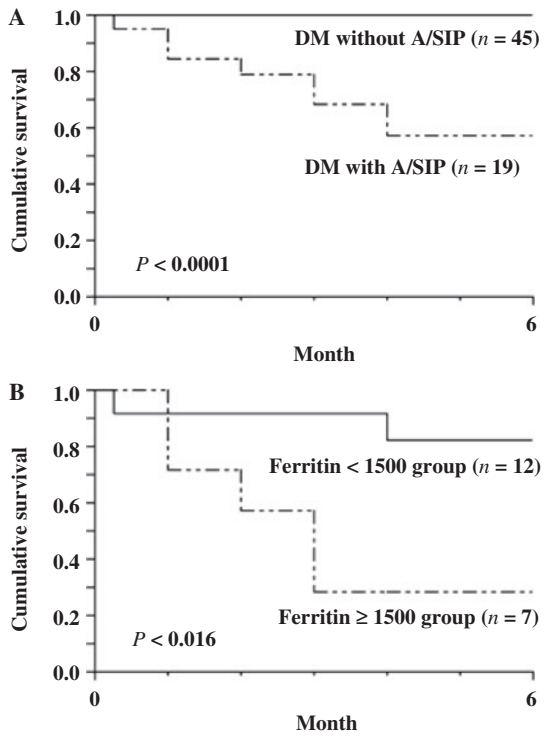
The *P*-value was estimated by the Fisher's exact test.

Table 4 Treatment in each group

Treatments	DM with A/SIP	DM with CIP	DM without ILD
No.	19	24	15
PSL alone, *n* (%)	3 (16)	9 (38)	12 (80)**
PSL + other agents, *n* (%)	16 (84)	15 (62)	3 (20)
CSA	7	5	0
IVCY	5	7	1
CSA or TAC + IVCY	4	0	0
MTX	0	2	0
IVIg	0	1	2

**$P < 0.01$ compared with DM with A/SIP using the Fisher's exact test. PSL: prednisolone; IVIg: intravenous immunoglobulin therapy.

Fig. 2 The cumulative survival rate for 6 months in each group (**A**), and serum ferritin <1500 ng/ml group and ⩾1500 ng/ml group of DM with A/SIP (**B**). DM without A/SIP, DM with CIP ($n = 24$) and DM without ILD ($n = 21$). The cumulative survival rate was calculated using the Kaplan–Meier test. The log-rank test was also used to compare survivals.



on muscle in PM [31]. Pathologically, macrophage activation has not yet been revealed in DM and PM.

On the other hand, the elevation of the serum ferritin level correlates with general disease activity of SLE [32–34]. We have experienced several cases in which serum ferritin was correlated with the activity of A/SIP with DM [Gono *et al*. (submitted)]. Additionally, we considered that a drop in ferritin concentration can predict a better pulmonary outcome in DM with A/SIP. Although it was not revealed whether elevated ferritin levels correlated with the activity of other clinical features such as dermatitis and myositis in the present study, serum ferritin may just be a marker of general disease activity rather than a specific marker for A/SIP. Additionally, the patients with A/SIP with DM had shorter disease duration than the other patients at the time the ferritin was investigated. The intensity of inflammation might correlate with serum ferritin concentration.

Several research efforts demonstrated that A/SIP was frequently complicated by C-ADM. Although C-ADM may be a useful indicator for the occurrence of A/SIP retrospectively, ILD with C-ADM does not always develop as a feature of A/SIP. It is possible that two different subsets of ILD with C-ADM may be A/SIP and CIP [12]. Our results indicate that muscle weakness was seen in 72% of the patients with DM and A/SIP, which means only 28% of the A/SIP with DM were C-ADM. Elevation of serum ferritin (⩾500 ng/ml) was seen in 63% of patients with DM and A/SIP. As a result of the comparison in the occurrence of A/SIP between the patients with DM showing serum ferritin levels <500 ng/ml and the patients with serum ferritin levels >500 ng/ml, the frequency of the complication with A/SIP was significantly higher in the group with levels >500 ng/ml (OR 6.9; 95% CI 2.1, 22.4). These results indicate that serum ferritin is much better as a marker to predict the A/SIP complication with DM than is C-ADM.

Survival in patients with DM with A/SIP differed significantly between patients with a high-baseline serum ferritin levels (⩾1500 ng/ml) and low-baseline ferritin levels ($P = 0.016$), which indicated that baseline serum ferritin concentrations could predict survival. Using the statistical method, we established a serum ferritin concentration cut-off value of 1500 ng/ml as the best indicator of survival in our cohort of patients with A/SIP with DM, with a sensitivity of 0.75 and a specificity of 0.91. As far as we are concerned, this is a high power of prediction for survival in patients with A/SIP with DM under conventional treatments.

In conclusion, serum ferritin concentration is a powerful indicator for the early diagnosis of A/SIP with DM and also predicts the disease severity and prognosis for patients with A/SIP. It is inferred from our findings that we should choose the intensive treatment using combination therapy with various immunosuppressant agents for patients with ILD with DM showing hyperferritinaemia, especially levels >1500 ng/ml.

Rheumatology key messages

- Serum ferritin is a useful predictor of the occurrence of acute interstitial pneumonia in DM.
- Serum ferritin concentration correlates with the prognosis of acute interstitial pneumonia in DM.

Acknowledgement

Funding: This work was supported by Research Grant from the Ministry of Health, Labour and Welfare in Japan.

Disclosure statement: The authors have declared no conflicts of interest.

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