Infection is not rare in patients with idiopathic inflammatory myopathies

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Abstract

Objective

To assess the prevalence and characteristics of infections in patients with idiopathic inflammatory myopathies (IIM) and analyse risk factors for infection using clinical presentation and biochemical findings of IIM.

Methods

Retrospective review of the medical records of patients with IIM followed up in a single medical centre from January 2008 to January 2018.

Results

Of the 779 patients with IIM, 215 (27.6%) suffered from infections. The prevalence of infection in dermatomyositis (DM) (29.8%) was more than polymyositis (PM) (18.5%). The lung was the most common infection site (66.5%). Multivariate analyses demonstrated that methylprednisolone pulse (MP) (OR=3.22; 95% CI=1.60-6.48; p=0.001), age of onset >50 years (OR=1.02; 95% CI=1.00-1.03; p=0.011), anti-melanoma differentiation-associated gene 5 (MDA5) antibody (OR=1.93; 95% CI=1.20-3.11; p=0.007), lymphocyte count <1200/mm^3 (OR=2.85; 95% CI=1.89-4.30; p<0.001), and interstitial lung diseases (ILD) (OR=2.03; 95% CI=1.30-3.71; p=0.002) are independent risk factors for infection. Survival analysis demonstrated that the three-year survival rate in the infection group was lower than the no-infection group (75.3% vs. 94.7%, p<0.001).

Conclusion

Among hospitalised individuals with IIM, infection is frequent and the leading cause of mortality. The anti-MDA5 antibody, lymphopenia, ILD, old age, and treatment with MP are contributing factors in the development of infections in patients with IIM.

Key words

infection, idiopathic inflammatory myopathies, dermatomyositis, polymyositis, anti-melanoma differentiation-associated gene 5 antibody

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Introduction

Idiopathic inflammatory myopathies (IIMs) are a group of clinically heterogeneous, autoimmune inflammatory muscular disorders characterised by muscular weakness and multisystem involvement (1, 2). The main clinical IIM subtypes in adults are polymyositis (PM) and dermatomyositis (DM).

Idiopathic inflammatory myopathies are associated with considerable mortality, with ten-year survival most recently estimated to be 50–90% (3-7). Infection has been described as one of the causes of mortality in patients with IIMs (8, 9). Given the rarity of the diseases, few studies have evaluated the burden of infections in patients with IIMs (10, 11). Recently, a large nationwide study from the US found that hospitalised patients with DM/PM experienced an infection had a 4.2-fold increased risk of death compared with no-infection. In particular, pneumonia, bacteraemia, and opportunistic fungal infections were significantly associated with mortality (8). However, few studies have elucidated the relationship between infections and IIM, and the risk factors for developing infection in IIM patients. The aims of the study were to investigate the prevalence, characteristics, and risk factors for infection in Chinese patients with IIM.

Patients and methods

Patient population

With the approval of the Research Review Committee (RRC) and the Ethical Review Committee (ERC) of the China-Japan Friendship Hospital, we retrieved medical records for patients who were hospitalised with the diagnosis of "PM" or "DM" from January 2008 to January 2018. A total of 779 consecutive patients with a diagnosis of DM (n=628) and PM (n=151) were included in the study. In the retrospective non-interventional study, all patients' data was anonymously used.

Data collection

Medical records were retrospectively collected for all patients. Variables of interest included age of onset, gender, disease duration, clinical features, laboratory test results from the first encounter, myositis specific antibodies (MSAs), complications at the time of patient admission, treatment, and cause of death.

The definition of infections

Infectious complications in patients were identified by clinical manifestations, imaging findings, and positive microbiological tests from blood, sputum, bronchoalveolar lavage (BAL) fluid culture and/or histological material (11).

Statistical analysis

Quantitative variables are reported as means and were compared using a non-parametric test. Categorical variables were reported as numbers and/or percentages and were compared using the chi-square or, when appropriate, Fisher exact test. Results from multivariate analysis were expressed as an odds ratio (OR) with 95% confidence interval (CI). A two-sided $p<0.05$ was considered to be statistically significant. Analyses were performed with SPSS Statistics for Windows, version 21.0 (IBM Corp., Armonk, NY, USA).

Results

IIM patient's demographics

In this study there were 779 patients with IIM (263 males, 516 females), with mean age of onset 46.4±15.6 years. Interstitial lung diseases (ILD) and malignant tumours were noted in 444 (57.0%) and 77 (9.9%) patients, respectively. Five hundred and forty (69.3%) patients presented with muscular weakness, 250 (32.1%) patients had arthralgia or arthritis, and 345 (44.3%) patients suffered from myalgia. About a quarter (26.2%) of the patients had dysphagia, and 291 (37.4%) patients presented with hypoventilation at disease onset. Anti-syntheses antibodies were the most common antibody in 162 (20.8%) patients, including 72 cases with Anti-histidyl (Jo-1) (9.2%), 39 cases with anti-threonyl (PL-7) (5%), 28 cases with anti-glycyl (EJ) (3.6%), 22 cases with anti-alanyl (PL-12) (3.2%) and one with anti-isoleucyl (OJ). Anti-melanoma differentiation-associated gene 5 (MDA5) antibodies were detected in 145 (18.6%) of patients. Also, 98 (12.6%) patients carried

anti-transcription intermediary factor 1γ (TIF1γ) antibodies, anti-MJ/nuclear matrix protein 2 (NXP-2) was identified in 68 (8.7%) patients, anti-signal recognition particles (SRPs) were identified in 50 (6.4%) patients, Mi-2 was identified in 40 (5.1%) patients, the anti-3-hydroxy-3-methylglutaryl coenzyme A reductase (HMGCR) autoantibody was identified in 32 (4.1%) patients, and the anti-small ubiquitin-like modifier-1 activating enzyme (SAE1) was identified in 15 (1.9%) patients.

Prevalence of infections

Among the 779 patients with IIM, 215 (27.6%) were identified as having infections. The prevalence of infection in DM and PM was 29.8% and 18.5%, respectively.

Characteristics of patients with IIM and infections

Based on the clinical data, an older age at onset was apparent in patients who developed infections (50.1 *vs*. 45.0 years; $p<0.001$; Table I). The prevalence of fever (35.8% *vs*. 24.3%; $p=0.002$) and Heliotrope rash (60.5% *vs*. 50.5%; $p=0.016$) was higher in the infection group than the no-infection group. The prevalence of ILD and hypoventilation was higher in patients with major infections than in those without infections (74.0% *vs*. 50.5%; $p<0.001$ and 48.8% *vs*. 33.0%; $p<0.001$), respectively. Conversely, the prevalence of PM and tumours was lower in the infection group than in the no-infection group. The infection and no-infection groups did not significantly differ in gender or the prevalence of dysphagia, muscular weakness, Gottron's rash, skin ulcer, arthritis/arthralgia, or myalgia. In terms of the IIM therapy regimen, the use of methylprednisolone pulse was significantly associated with infections (13.5% *vs*. 3.9%; $p<0.001$).

Comparisons of biochemical variables indicated that patients with infections had lower peripheral blood absolute lymphocyte counts (1062.4 *vs*. 1478.4 counts/mm^3; $p<0.001$) and higher levels of serum ferritin (864.4 *vs*. 525.2 ng/ml; $p<0.001$) than those without infections. The prevalence of patients with elevated levels of aspartate aminotransferase (AST), alanine transferase (ALT) lactate dehydrogenase (LDH), erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP) in patients with infections was greater than those without infections (all $p<0.05$). However, the prevalence of elevated creatine kinase (CK) levels did not differ between the infection and non-infection groups.

Table I. Comparison of the characteristics of patients with IIM and with and without infections.

Characteristics	Infections (n=215)	No infections (n=564)	*p*-value
Male/Female	64/151	199/365	0.15
Onset age (years)	50.1	45.0	<0.001
DM	187/215 (87.0%)	441/564 (78.2%)	0.006
PM	28/215 (13.0%)	123/564 (21.8%)	0.006
ILD	159/215 (74.0%)	285/564 (50.5%)	<0.001
Tumour	12/215 (5.6%)	65/564 (11.5%)	0.015
Heliotrope rash	130/215 (60.5%)	285/564 (50.5%)	0.016
Gottron rash	108/215 (50.2%)	265/564 (47.0%)	0.424
Skin ulcer	27/215 (12.6%)	49/564 (8.7%)	0.078
Arthritis/arthralgia	65/215 (30.2%)	185/564 (32.8%)	0.548
Myalgia	95/215 (44.2%)	250/564 (44.3%)	1.0
Muscle weakness	150/215 (69.8%)	390/564 (69.1%)	0.931
Dysphagia	64/215 (29.8%)	140/564 (24.8%)	0.172
Hypoventilation	105/215 (48.8%)	186/564 (33.0%)	<0.001
Fever	77/215 (35.8%)	137/564 (24.3%)	0.002
Lymphocyte(counts/mm^3)	1062.4	1478.4	<0.001
Ferritin (ng/ml)	864.4	525.2	<0.001
Elevated CK (>200IU/L)	81/199 (40.7%)	235/553 (42.5%)	0.41
Elevated LDH (>250IU/L)	143/199 (71.9%)	287/530 (54.2%)	<0.001
Elevated ALT (>40IU/L)	118/203 (58.1%)	263/542 (48.5%)	0.02
Elevated AST (>40IU/L)	116/203 (57.1%)	223/532 (41.9%)	<0.001
Elevated ESR (>20mm/h)	99/189 (52.3%)	181/520 (34.8%)	<0.001
Elevated CRP (>0.8mg/L)	83/191 (43.5%)	142/508 (28.0%)	<0.001
Methylprednisolone pulse	29/215 (13.5%)	22/564 (3.9%)	<0.001

As shown in Figure 1, the infection rate was 68/145 (46.9%) in the MDA5 antibody group, 25/68 (36.8%) in the NXP-2 antibody group, 5/15 (33.3%) in the SAE1 antibody group, 12/39 (30.8%) in the PL-7 antibody group, 8/28 (28.6%) in the EJ antibody group, 6/22 (27.3%) in the PL-12 antibody group, 13/50 (26%) in the SRP antibody group, 10/40 (25%) in the Mi-2 antibody group, 8/32 (25%) in the HMGCR antibody group, 19/98 (19.4%) in the TIF1γ antibody group, and 9/72 (12.5%) in the Jo-1 antibody group.

Comparisons of different myositis-autoantibodies between the infection and no-infection groups indicated that the anti-MDA5 antibody was more common among patients with *vs*. without infection (31.6% *vs*. 13.7%; $p<0.001$). Conversely, the presence of the anti-Jo-1 antibody was less common among patients with *vs*. without infection (4.2% *vs*. 11.2%; $p=0.002$) (Table II). No significant differences were found between the infection and no-infection groups with regards to the following antibodies: anti-PL-7, anti-PL-12, anti-EJ, anti-TIF1-γ, anti-Mi-2, anti-NXP-2, anti-SRP, anti-HMGCR, and anti-SAE1 antibody.

Site of infection and type of micro-organism

Pulmonary infection was the most common infection (66.5%), followed by bacteraemia without focus (10.2%), upper respiratory tract infection (8.8%), urinary tract infection (5.6%), skin-soft tissue infection (3.7%), digestive tract infection (3.5%), and other infection (1.7%). Furthermore, lung infection accounted for 92.6% (63/68) of infections among patients with MDA5-DM.

Of the microbiologically documented infections, the most common micro-organisms infecting patients with IIM were *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Mycoplasma pneumoniae*, followed in frequency by *Escherichia coli*, *Staphylococcus aureus*, and *Pseudomonas aeruginosa*. Six patients developed *M. tuberculosis* infections. Among the patients infected with a virus, 23 patients were infected with

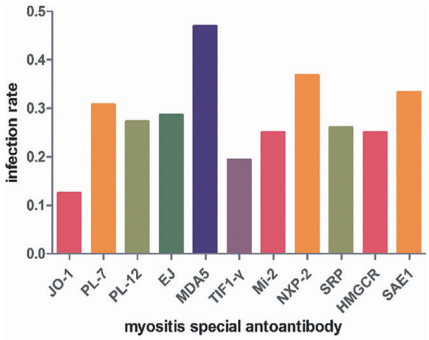

Fig. 1. The prevalence of infection in different myositis antibodies.

Table II. Distribution of MSAs in patients with IIM and with and without infections.

Type of antibody	Infections (n=215)	No infections (n=564)	*p*-value
Jo-1	9/215 (4.2%)	63/564 (11.2%)	0.002
PL-7	12/215 (5.6%)	27/564 (4.8%)	0.713
PL-12	6/215 (2.8%)	16/564 (2.8%)	1.0
EJ	8/215 (3.7%)	20/564 (3.5%)	1.0
MDA-5	68/215 (31.6%)	77/564 (13.7%)	<0.001
Tif-1γ	19/215 (8.8%)	79/564 (14.0%)	0.054
NXP-2	25/215 (11.6%)	43/564 (7.6%)	0.088
Mi-2	10/215 (4.7%)	30/564 (5.3%)	0.856
SRP	13/215 (6.0%)	37/564 (6.6%)	0.871
HMGCR	8/215 (3.7%)	24/564 (4.3%)	0.842
SAE1	5/215 (2.3%)	10/564 (1.8%)	0.616

cytomegalovirus (CMV), 13 patients were infected with CMV and EBV, six patients were infected with EBV, and five patients were infected with *Herpes simplex virus* (HSV). Fungal infections were the other major opportunistic infections. Five patients were infected with invasive *Aspergillus* infections, there were 15 cases of Candida, and 28 cases of *Pneumocystis jirovecii pneumonia* (PJP) with or without other fungal infection.

Pneumocystis jirovecii pneumonia (PJP) in IIM

There was a total of 28 cases of IIM with PJP, including 27 with DM (96.4) and one with PM (3.6%). Twenty-four (85.7%) patients were diagnosed by BAL fluid. Twenty-two (78.6%) patients developed PJP within six months of onset of the disease. Anti-MDA5 antibodies occurred more frequently in patients with DM and PJP than those without PJP (40.7% *vs*. 17.5%, p=0.008).

Risk factors for infection in IIM

According to univariate analysis result, several significant factors were selected for multivariate analysis to identify independent predictive factors for the infections in IIM patients.

Multivariate analyses revealed that, compared with patients without an infection, patients with an infection were treated more frequently with pulsed methylprednisolone (OR=3.22; 95% CI=1.60–6.48; p=0.001). Furthermore, age at onset >50 years (OR=1.02; 95% CI=1.00–1.03; p=0.011), anti-MDA5 antibody (OR=1.93; 95% CI=1.20–3.11; p=0.007), ILD (OR=2.03; 95% CI=1.30–3.71; p=0.002), and lymphocyte count <1200/mm^3 (OR=2.85; 95% CI=1.89–4.30; p<0.001) also remained as independent risk factors for major infections.

Survival analysis

- Predictors of mortality in hospitalisations

The characteristics of patients with IIM who survived and died, as well as analyses of the predictors of mortality, are displayed in Figure 2. Generalised Estimated Equation (GEE) analysis revealed that infection (OR=7.33; 95% CI=4.58–11.75), malignancy (OR=5.56; 95% CI=2.78–11.12), skin ulcer rash (OR=3.03; 95% CI=1.60–5.74), and ILD (OR=1.66; 95% CI=1.01–2.74) were four factors that independently predicted the in-hospital mortality of patients with IIM.

- Probability of survival in patients with and without infection

Kaplan-Meier survival curves indicate the probability of survival for patients with and without infection. Survival analysis demonstrated that the infection group's three-year survival rate was lower than that of the non-infection group (75.3% *vs*. 94.7%, p<0.001) (Fig. 3). Since IIM diagnosis, the survival of the cohort without infection was 97.5% at three months, 97.2% at six months, 96.3% at one year, and 95.2% at two years. However, after the first episode of infection, survival declined sharply to 87.4% at three months, 82.3% at six months, 78.1% at one year, and 76.7% at two years. Compared with patients with DM and without PJP, those with PJP had a higher mortality rate (44.4% *vs*. 7.1%, p<0.001).

Discussion

In this study, we observed that infection was the leading cause of mortality in patients with IIM, and 27.6% of patients with IIM developed infections in our cohort. The prevalence of infection was more common in patients with DM as compared with patients with PM. The lung was a frequent site of infection, and opportunistic infections comprised about one-third of all infectious episodes. Patients with IIM that had the anti-MDA5 antibody, lymphopenia, ILD, old age at onset, or were treated with a methylprednisolone pulse tended to have a higher risk of infection.

Infectious complications have been frequently reported in patients with CTDs. However, more attention has been paid to patients with SLE, Wegener's granulomatosis, and RA in the past decades. Only a few studies investigating patients with IIM were published, most of which had small sample sizes. Previous studies found the frequency of infection in patients with IIM was 25–33% (12). This large study demonstrated that the prevalence of infections in patients with IIM was 27.6%.

A Chinese study by Chen *et al*. demonstrated that bacteria were the major pathogens in patients with IIM and infection, including *Klebsiella, Acinetobacter, Staphylococcus, E. coli* and *Salmonella* (11). In this study, we also found that *Klebsiella pneumoniae, Acinetobacter baumannii, Mycoplasma pneumoniae*, accounted for the majority of bacterial infections. Previous reports indicated that opportunistic infections occurred in 10.9–21.3% of patients with PM/DM (12-15). To date, the largest study found that 180/15407

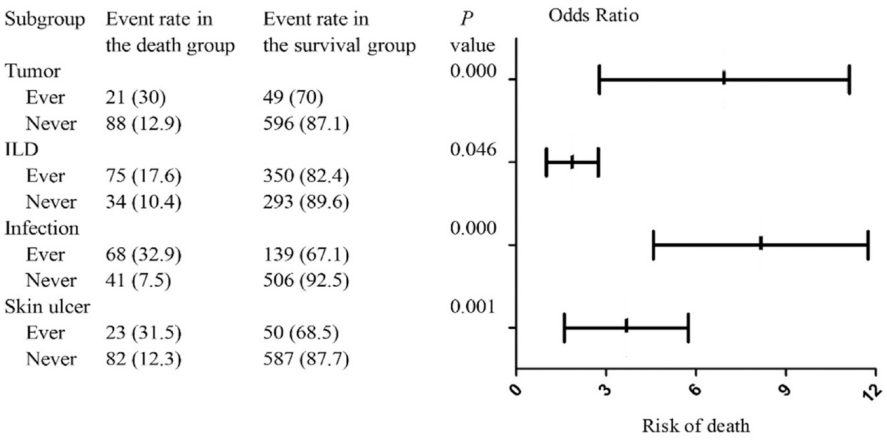

Fig. 2. Independent risk factors of in-hospital mortality identified by multivariate analyses.

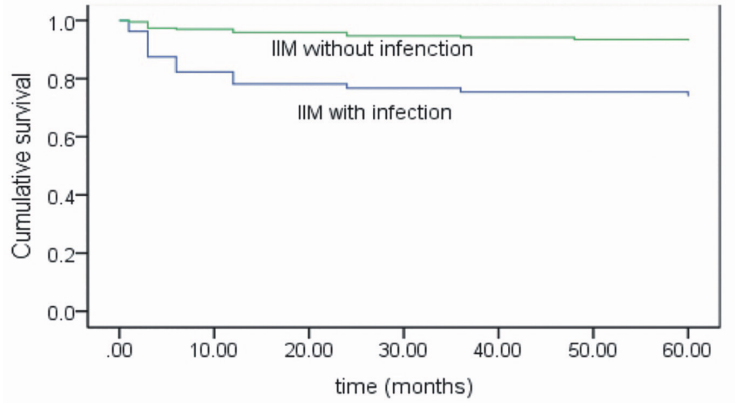

Fig. 3. Survival curves for IIM patients with and without infection.

(1.2%) patients with IIM had opportunistic fungal infections (8). In our cohort, the prevalence of opportunistic infections was 10.4%, and obviously higher than that of American patients with IIM and European cohort (16).

In this study, only six (0.8%) patients with IIM suffered from mycobacterial infection. This prevalence was similar to the study from the US. However, the possibility of mycobacterial infection has to be kept in mind because of treatment with high doses of steroids and/or immunosuppressive drugs (17).

One study found that CMV reactivation might occur more frequently in patients with DM than previously recognised (18). Thirty-six patients in this study had CMV infections, which constituted the most common pathogen among viral infections. Takizawa *et al*. studied the clinical characteristics of CMV infection in patients with rheumatic disease and found that 15 (10.1%) patients had DM, and seven (46.7%) of the 15 patients with DM died (19). Another Chinese study reported that the group of patients with DM that were infected with CMV, and their rates of pulmonary interstitial fibrosis and mortality were higher than in patients without CMV infection (20).

Pneumocystis jirovecii pneumonia is an opportunistic fungal pathogen which rarely causes symptomatic infections in the immunocompetent population but can cause severe infections, most commonly pneumonia, in immunocompromised hosts (21, 22). Ward *et al*. reported the frequency of PJP to be 27 per 10,000 hospitalisations (23) while Godeau *et al*. estimated the frequency to be 20/10,000 patient-years in patients with IIM (24). A meta-analysis, including the reports noted above, found that 6% (40/688) of patients with DM/PM developed PJP (25). Like other studies, the current study identified 28 cases of PJP throughout the study period. Furthermore, patients with IIM that were infected with *P. jirovecii* had a high mortality rate. About half of these patients died of PJP.

Studies have found that the cumulative mortality at one and five years after diagnosis with IIM was 9% and 23%, respectively (3). However, after the first episode of major infection in Chinese IIM patients, survival declined sharply to 84.7% at 30 days and 68.3% at one year (11). In the current study, patients with IIM who had experienced infection had a one-year cumulative survival rate of 78.1%, which indicates that patients with IIM who experience infection have a poorer prognosis than the general population of patients with IIM. Through an analysis of causes of death, we also found that infection was the leading cause of death.

Predictors of infection are always a concern in patients with IIM, given their associations with morbidity and mortality. In our cohort, patients with IIM with anti-MDA5 antibodies and ILD were more prone to infection. Interestingly, we also found that patients with IIM that carried the anti-Jo-1 antibody had less risk of infection. This may indicate that patients with IIM that test positive for the anti-Jo-1 antibody are relatively mild condition, as only a small percentage of them develop an infection. However, this finding warrants further investigation.

This study found that total lymphocyte count <1200/mm^3 was a risk factor for infection. Researchers have established that lymphopenia is a contributing factor in the development of opportunistic infection in IIM, including severe and fatal infection with PJP and CMV (20, 26). Takizawa *et al*. suggested that a higher age (>59.3 years), presence of symptoms, and lymphopenia may signal the time to initiate anti-CMV therapy (19). Thus, we recommend monitoring peripheral blood lymphocyte counts when following up with patients with IIM (11, 24, 26). Prophylaxis should also be considered in patients with CTD who are undergoing intense immunosuppressive therapy (27, 28), especially if they have lymphopenia or a low CD4 count (26). In addition, prophylaxis should be recommended for infections in patients with IIM.

Steroids are by far the most widely discussed risk factor for infection in the

literature. Our study found that methylprednisolone pulse was the greatest risk factor for infection (OR=3.22). Several studies of patients with IIM demonstrated that systemic glucocorticoid therapy and high mean daily doses of steroids were associated with increased risk of opportunistic infections (13, 29). Therefore, we do not recommend long-term use of large doses of glucocorticoids in patients with IIM.

The present study has several limitations. First, it was a retrospective, single-centre study, by the nature of a retrospective, selection bias might have played a role. Second, immunosuppressive therapy, the presence of calcinosis, disease activity, the time since the diagnosis of myopathy, number of hospitalisation days, the need of intensive care unit admission, and mechanical invasive ventilation due to serious ILD, all of which are known risk factor for infections. However, these factors are not further analysed in this study. Third, in addition to infection, neoplasia, disease activity and cardiovascular disease are risk factors of mortality.

In conclusion, this study revealed a high frequency of infections in patients with IIM, which were also a leading cause of mortality. Patients who were older at the time of IIM onset, who had the anti-MDA5 antibody, lymphopenia, or ILD, or underwent methylprednisolone pulse therapy tended to have a higher frequency of infection. However, other factors may increase the risk of infection, and further studies will be needed. Strategies to lower infection risk in patients with IIM should be evaluated to improve disease outcomes.

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