ORIGINAL ARTICLE

A review of idiopathic inflammatory myopathy cases in Terengganu, Malaysia: A single centre experience

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ABSTRACT
Introduction: The purpose of this study was to analyse the clinical characteristics of patients with idiopathic inflammatory myopathy (IIM) in Hospital Sultanah Nurzahirah (HSNZ), Terengganu, Malaysia. It also aimed to describe the disease manifestations in association with malignancy and other CTD.

Methods: This was a retrospective descriptive study involving all IIM patients who were managed by the Rheumatology Unit HSNZ from January 2010 to December 2019.

Results: In this review we described 15 cases wherein malignancy was detected in 4 patients after the diagnosis of IIM was made and 4 patients with overlap syndrome. One third of patients with malignancy and overlap syndrome had poor treatment response and succumbed to complications of the disease. Almost all of patients received corticosteroid as the first line therapy and nearly two thirds of them responded well to either corticosteroid alone or with combination therapy.

Conclusion: Although this study did not represent the whole population in Malaysia, it provides a better understanding of the disease manifestation, treatment and disease complications in our cohort of patients.

KEYWORDS:
Myositis, Idiopathic Inflammatory Myopathy, Malignancy, Connective Tissue Disease

INTRODUCTION
Idiopathic inflammatory myopathy (IIM), also known as myositis, is a rare heterogeneous autoimmune disorder that leads to proximal myopathy and extra muscular manifestations, and may be part of a paraneoplastic syndrome.¹ The 119th European Neuromuscular Centre (ENMC) international workshop divides IIM into polymyositis (PM), dermatomyositis (DM), inclusion body myositis (IBM), non-specific myositis and immune mediated necrotizing myopathy.¹ The disease prevalence is 5 to 22 per 100,000 population with approximately 1.2 to 19 million persons at risk per year.² Most of the epidemiological studies on IIM are from Northern Europe and data for the Asian population is still lacking.³

The association between IIM and malignancy or other connective tissue diseases (CTD), is well known. However, there is a paucity of data pertaining to this association in Asian countries.¹ The pathophysiology of malignancy-associated IIM is still unclear but is hypothesized to be due to the autoimmune response to internal malignancy.⁴ The risk of malignancy in IIM is 2 to 7 times higher than in the general population, particularly with DM.⁴ A few meta-analyses showed that the risk for malignancy in IIM was significantly higher within the first year of diagnosis and remains high up to 5 years after IIM onset.⁵,⁶ Based on studies among Norwegian and Chinese cohorts, the most commonly encountered malignancies were lung, ovarian and breast cancer in DM, non-Hodgkin lymphomas, lung and bladder cancer in PM, and prostate, colorectal, and haematological malignancies in IBM.⁷,⁸

Even though multiple clinical and laboratory features have been associated with malignancy in IIM and various malignancy screening strategies have been proposed, they remain to be proven. Malignancy screening should be performed in all IIM patients based on risk stratification including age and sex. A comprehensive history and physical examination including rectal, breast, pelvic and testicular examination, and basic laboratory testing should be performed in all IIM patients.⁹ Studies on the use of tumour markers in clinical practice showed that they have a high false-positive and poor sensitivity rate, thus their ability to diagnose malignancy is still controversial.¹⁰,¹¹ A large DM cohort with 400 patients showed a blind assessment with computed tomography (CT) imaging was able to reveal malignancy in 59% of patients and the majority of them were asymptomatic.¹²

As IIM is often considered to be a paraneoplastic syndrome, a recommendation for malignancy screening has been adopted from the European Federation of the Neurological Societies (EFNS) task force. EFNS recommends primary screening with CT of the chest/abdomen/pelvis, pelvic ultrasound and mammography in women, ultrasound of the testes in men, and colonoscopy in men and women over 50 years of age. The task force also recommends for a repeat screening annually for 3 years and to proceed with further screening if new symptoms or clinical findings emerge.¹³ IIM patients with malignancy also showed significant complications that contribute to a higher mortality rate.¹⁴
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Some of the myositis-specific antibodies (MSA), particularly anti-TIF1 gamma, anti-NXP-2, and anti-SA E1 had been identified to be highly specific for malignancy-related IIM but none of the MSA is associated with a specific type of malignancy. The risk of malignancy is low in patients positive for anti-Mi-2, anti-SRP, anti-MDA5, anti-PL-7, anti-EJ, or anti-OJ antibodies.12 Whereas, myositis-associated antibody (MAA) is found in CTD-related IIM.7

In this study, we analysed the baseline characteristics and demographic data of IIM patients in Terengganu, Malaysia and described the disease manifestations in association with malignancy and other CTD.

MATERIALS AND METHODS
This was a retrospective descriptive study involving all IIM patients who were managed by the Rheumatology Unit Hospital Sultanah Nurzahirah (HSNZ), Terengganu, Malaysia from January 2010 to December 2019. The study proposal was reviewed and approved by the National Medical Research Register (NMRR) (research and ethics approval ID NMRR-19-3433-52063). All IIM patients from the Rheumatology Clinic HSNZ were recruited into this study. The inclusion criteria were patients: (i) diagnosed with IIM based on the ENMC Classification criteria3; and (ii) aged 18 years and older. The exclusion criteria were patients: (i) who were on lipid lowering agents or other medications that can induce myositis; (ii) with endocrine or metabolic disorders such as hypokalaemia, thyroid disorder and Cushing syndrome; and (iii) with muscle trauma.

Demographic data such as age and gender, data on disease manifestation and duration, investigations and medications were retrieved from the Hospital Information System (HIS) and recorded in the data collection sheet. The data were expressed as mean ± standard deviation (SD) unless otherwise stated.

RESULTS
Demographic and clinical features
A total of 15 patients were included in this study, the majority of whom were women (73.3%). The median age of diagnosis was 44 years and the median disease duration was 24 months. The median duration of symptoms prior to the diagnosis was 8 weeks. Nine patients (60%) were diagnosed with PM, 3 (20%) with dermatomyositis (DM/PM), 2 (13.3%) with necrotizing autoimmune myositis (NAM) and 1 (6.7%) with DM. Fourteen cases (93.3%) presented with proximal myopathy, all of whom had elevated serum creatinine kinase (CK). The highest CK level documented was 46,000 IU/L. Nearly half of the patients (46.6%) had extramuscular manifestations; mainly dysphagia (26.7%), interstitial lung disease (20%) and arthritis (13.3%). Heliotrope rash (20%),shawl sign (20%) and periorbital oedema (20%) were the most common skin manifestations; Gottron papules and V sign were the other manifestations.

Investigations finding
All patients except one underwent electromyography (EMG) as part of the investigation and 12 (80%) had typical myopathic EMG findings such as increased membrane irritability and spontaneous fibrillations. The EMG reports of the remaining 2 patients (13.3%) were not available. Six patients underwent muscle biopsy but only 26.7% had features consistent with inflammatory myositis. Five (33.3%) patients had myositis antibody testing but only 2 had positive autoantibodies; a patient with necrotizing autoimmune myositis which was positive for anti-Ku, anti-Ro and anti-SRP and a patient with overlap polymyositis and scleroderma which was positive for anti-TIF1 gamma. Five (33.3%) patients underwent magnetic resonance imaging (MRI) of the muscle and the finding was consistent with active myositis. The investigations performed are shown in Figure 1 and Table I.

Association with malignancy
All patients were screened for malignancy except one, as this patient defaulted our follow up. The malignancy screening included upper and lower gastrointestinal (GI) scopes, tumour markers, computed tomography of the neck, thorax, abdomen and pelvis (CT NTAP), mammogram, gynaecology and ENT assessment. Four patients (26.7%) had underlying malignancy, which was detected after the diagnosis of IIM. The details are shown in Table I.

Case 12 was diagnosed to have recurrence of ovarian cancer two months after the diagnosis of PM/DM. The patient had previous ovarian cancer in complete remission for the preceding 20 years and presented with new onset of symmetrical proximal muscle weakness, skin lesions and dysphagia. The patient had significantly elevated CK and LDH levels with a positive skin biopsy. Unfortunately, the patient had poor treatment response and succumbed to advanced malignancy.

Case 13 was diagnosed with PM/DM, followed by left breast carcinoma 3 months later. The patient also had the typical clinical features of IIM, and the malignancy screening confirmed the diagnosis of left breast carcinoma. The patient did not respond to treatment and succumbed due to malignancy complications.

Case 15 presented only with a skin lesion without proximal myopathy and the diagnosis of colon adenocarcinoma was made after seven months. The patient had no GI or constitutional symptoms but colonoscopy showed a rectal mass and biopsy confirmed adenocarcinoma of the colon. The patient showed a good treatment response after the tumour removal and a course of cancer chemotherapy along with the CS to control the skin lesion.

Case 14 was diagnosed to have papillary thyroid cancer 3 months after the diagnosis of PM. The patient had typical clinical manifestations of PM, underwent thyroidectomy and responded well to CS therapy.

Association with other CTDs
There were four cases (26.7%) that overlapped with another CTD; three cases (Case 8, Case 9, and Case 10) had SSc and one case (Case 11) had SLE.

Treatment and treatment response

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<table>
<thead>
<tr>
<th>Case</th>
<th>Age at diagnosis (years)</th>
<th>Manifestation</th>
<th>Investigation</th>
<th>Diagnosis</th>
<th>Malignancy</th>
<th>Time to diagnosis of malignancy</th>
<th>Treatment and treatment response</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>45</td>
<td>Symmetrical proximal myopathy, no extra-muscular involvement</td>
<td>Elevated CK (1052 IU/L) and LDH (233 IU/L), positive EMG and muscle biopsy</td>
<td>Polymyositis</td>
<td>Nil</td>
<td>Not applicable</td>
<td>CS and MTX Good response</td>
</tr>
<tr>
<td>2</td>
<td>41</td>
<td>Symmetrical proximal myopathy, no extra-muscular involvement</td>
<td>Elevated CK (5000 IU/L), positive EMG and muscle biopsy</td>
<td>Polymyositis</td>
<td>Nil</td>
<td>Not applicable</td>
<td>CS, AZA and MTX Good response</td>
</tr>
<tr>
<td>3</td>
<td>55</td>
<td>Symmetrical proximal myopathy and arthralgia</td>
<td>Elevated CK (389 IU/L) and LDH (451 IU/L), others not available</td>
<td>Polymyositis</td>
<td>Nil</td>
<td>Not applicable</td>
<td>CS Died from severe infection</td>
</tr>
<tr>
<td>4</td>
<td>44</td>
<td>Symmetrical proximal myopathy and ILD</td>
<td>Elevated CK (4672 IU/L) and LDH (1100 IU/L), positive EMG and MRI thigh, muscle biopsy</td>
<td>Polymyositis</td>
<td>Nil</td>
<td>Not applicable</td>
<td>CS, MTX, AZA, MMF, IVlg Good response</td>
</tr>
<tr>
<td>5</td>
<td>47</td>
<td>Symmetrical proximal myopathy, no extra-muscular involvement</td>
<td>Elevated CK (1405 IU/L) and LDH (402 IU/L), positive EMG and muscle biopsy, normal MRI thigh</td>
<td>Polymyositis</td>
<td>Nil</td>
<td>Not applicable</td>
<td>CS, AZA and MTX Good response</td>
</tr>
<tr>
<td>6</td>
<td>23</td>
<td>Symmetrical proximal myopathy, no extra-muscular involvement</td>
<td>Elevated CK (6758 IU/L) and LDH (837 IU/L), positive EMG (consistent with necrotizing autoimmune myositis), positive anti-SRP, anti-RO and anti-KU</td>
<td>Necrotizing autoimmune myositis</td>
<td>Nil</td>
<td>Not applicable</td>
<td>CS and MTX Good response</td>
</tr>
<tr>
<td>7</td>
<td>28</td>
<td>Symmetrical proximal myopathy, no extra-muscular involvement</td>
<td>Elevated CK (46000 IU/L) and LDH (843 IU/L), positive EMG (consistent with necrotizing autoimmune myositis), negative MSA/MAA</td>
<td>Necrotizing autoimmune myositis</td>
<td>Nil</td>
<td>Not applicable</td>
<td>CS and MTX Good response</td>
</tr>
<tr>
<td>8</td>
<td>22</td>
<td>Symmetrical proximal myopathy, skin tightening and dysphagia (consistent with scleroderma)</td>
<td>Elevated CK (5460 IU/L), positive MRI thigh, negative MSA/MAA</td>
<td>Overlap, Polymyositis and Scleroderma</td>
<td>Nil</td>
<td>Not applicable</td>
<td>CS, MTX (ceased due to lung fibrosis), AZA Good response</td>
</tr>
<tr>
<td>9</td>
<td>38</td>
<td>Symmetrical proximal myopathy and dysphagia</td>
<td>Elevated CK (786 IU/L) and LDH (960 IU/L), positive EMG and skin biopsy, positive anti-TIF1 gamma</td>
<td>Overlap, Dermatomyositis and Scleroderma</td>
<td>Nil</td>
<td>Not applicable</td>
<td>CS and MTX Good response</td>
</tr>
<tr>
<td>10</td>
<td>24</td>
<td>Symmetrical proximal myopathy, dysphagia, skin tightening</td>
<td>Elevated CK (3670 IU/L) and LDH (1080 IU/L), positive EMG, muscle biopsy and MRI thigh</td>
<td>Overlap, polymyositis and scleroderma</td>
<td>Nil</td>
<td>Not applicable</td>
<td>CS, AZA, MTX, CYC, IVlg, MMF, Rituximab Died from severe pulmonary hypertension</td>
</tr>
<tr>
<td>11</td>
<td>33</td>
<td>Symmetrical proximal myopathy and arthritis</td>
<td>Elevated CK (9748 IU/L), others not available</td>
<td>Overlap, Polymyositis and SLE</td>
<td>Nil</td>
<td>Not applicable</td>
<td>Unsure (defaulted follow up)</td>
</tr>
<tr>
<td>12</td>
<td>75</td>
<td>Skin lesion, facial swelling, symmetrical proximal myopathy and dysphagia</td>
<td>Elevated CK (426 IU/L) and LDH (487 IU/L), positive skin biopsy, normal EMG</td>
<td>Polymyositis and Dermatomyositis</td>
<td>Yes, Recurrence of ovarian cancer</td>
<td>2 months</td>
<td>CS Died from advanced malignancy</td>
</tr>
<tr>
<td>13</td>
<td>70</td>
<td>Symmetrical proximal myopathy, periocular edema and rashes, no extra-muscular involvement</td>
<td>Elevated CK (3900 IU/L) and LDH (602 IU/L), positive MRI thigh, normal EMG, no evidence of DM on skin biopsy</td>
<td>Polymyositis and Dermatomyositis</td>
<td>Yes, left breast invasive carcinoma</td>
<td>3 months</td>
<td>CS, IVlg Died from severe infection</td>
</tr>
<tr>
<td>14</td>
<td>68</td>
<td>Symmetrical proximal myopathy, no extra-muscular involvement</td>
<td>Elevated CK (8130 IU/L) and LDH (1519 IU/L), positive EMG and muscle biopsy</td>
<td>Polymyositis and Dermatomyositis</td>
<td>Yes, metastatic papillary thyroid cancer</td>
<td>3 months</td>
<td>CS Good response</td>
</tr>
<tr>
<td>15</td>
<td>70</td>
<td>Skin lesion, no proximal myopathy</td>
<td>Normal CK and LDH, positive skin biopsy</td>
<td>Dermatomyositis</td>
<td>Yes, adenocarcinoma of colon</td>
<td>7 months</td>
<td>CS Good response</td>
</tr>
</tbody>
</table>

CK = creatinine kinase, LDH = lactate dehydrogenase, EMG = electromyography, MRI = magnetic resonance imaging, ILD = interstitial lung disease, MSA = myositis-specific antibody, MAA = myositis-associated antibody, CS = corticosteroids, MTX = methotrexate, AZA = azathioprine, MMF = mycophenolate mofetil, IVlg = intravenous immunoglobulin, DM = dermatomyositis
All patients except one received corticosteroid (CS) as first line therapy and two patients (Case 14 and Case 15) responded well with corticosteroid alone. Patients who received a combination of corticosteroid and other immunosuppressive therapies (Case 1, Case 2, Case 5, Case 6, Case 7, Case 8 and Case 9) showed good treatment response and subsequently achieved disease remission.

The majority of the patients received either methotrexate (MTX) (60%) or azathioprine (AZA) (33.3%) as the second line agent. Other second line agents given to the patients included myophenolate mofetil (MMF), intravenous immunoglobulin (IVIg) and biologic therapy. IVIg was given as induction therapy for our refractory cases (Case 4 and Case 10) and when other immunosuppressive drugs were contraindicated (Case 13).

Nine patients (60%) responded well to their therapy and showed significant improvement of their symptoms and CK level. However, 4 patients (26.7%) (Case 3, Case 11, Case 12 and Case 13) had poor disease control despite a good dose of corticosteroid and immunosuppressant therapy, three of whom had secondary malignancy and SSc. The patients succumbed to disease complications such as infection, advanced malignancy and severe pulmonary hypertension.

DISCUSSION
The results of our case review are consistent with the previous Caucasian and Asian study that showed that IIM is a female predominant disease with a median age at diagnosis within the fourth decade of life.5

This review also demonstrated that more than half of the patients were diagnosed with malignancy or had overlap CTD. Four patients who were subsequently found to have cancer had IIM as the paraneoplastic manifestation. The patients with malignancy were detected within 2 to 7 months of their IIM diagnosis. Even though the number of patients in this study was small, our findings suggested that IIMs can be an early sign of malignancy. A study by Chow et al showed that the cancer risk was six-fold higher during the first year of the IIM diagnosis and lower during subsequent years of follow up.16 Thus, monitoring of emerging malignancy related local/systemic symptoms during each clinic visit is very important for the first 5 years of diagnosis and this can be up to 20 years after the IIM diagnosis.6

Majority of our patients responded well with corticosteroid therapy with combination of second line treatment. Most of the existing studies recommended CS as the first line therapy. However, there was no specific recommendation for the dose and duration of the CS treatment regime.18,19 Therefore, the decision for tapering of therapy was based on clinical and biochemical response.

Our patients who received a combination of corticosteroid and other immunosuppressive therapies showed good treatment response and subsequently achieved disease remission. This finding was similar to a previous study by Souza et al, who reported that individuals who received methotrexate or/and azathioprine showed an improvement in functional status and required lower maintenance CS doses. The survival rate of patients with malignancy or CTD related disease is known to be very poor.17 Thus, all IIM patients should be evaluated for malignancies at diagnosis, followed by long-term surveillance for a better therapy and outcome.

Although muscle biopsy is the gold standard for the diagnosis of IIM, only 6 patients had muscle biopsy due to logistic limitations of the procedure, with only 26.7% demonstrating features consistent with inflammatory myositis. Bohan et al reported that 10-20% of patients with IIM may have normal muscle biopsy findings and the absence of inflammatory infiltrates does not exclude IIM.20,21 The negative muscle biopsy results could be due to sampling error owing to skip lesions or treatment with CS prior to biopsy sampling.22,23 The diagnostic yield can be improved with MRI guided muscle biopsy for a better interpretation. Having said that, we arranged for muscle biopsy in patients with recurrent relapses or poor treatment response before deciding on further treatment options.

As reported in previous studies, MSA assists in risk stratification for malignancy screening in IIM patients as certain MSA act as biomarkers for malignancy.12,13 Only 33.3% of our patients had myositis antibody testing due to limited resources, mainly because it had to be done in a private laboratory. Anti-SRP autoantibodies have been
shown to be significantly associated with necrotizing autoinmune myositis\(^1\) and it was positive in one of our patients. Although the patient had no extra-muscular involvement and responded well to immunosuppressive therapy at the time of this study period, the patient should continue to be monitored closely as anti-SRP positive patients are generally reported to have poor treatment response.\(^2\)

Another patient with overlap of polymyositis and scleroderma was positive for anti-TIF1 gamma but had no evidence of malignancy at the time of this study period. This patient required regular monitoring and screening for the possibility of malignancy in the future.

Most of our patients were diagnosed by their typical clinical manifestations, elevated muscle enzymes and EMG and/or antibody myositis panel. As proposed by David et al.\(^2\), patients with the classical clinical features of IM, elevated serum CK and typical neurophysiological changes on EMG do not need a confirmatory muscle biopsy, unless management difficulties arise.

CONCLUSION

Although our study population was small and dominated by one ethnicity (Malays), it does illustrate the spectrum of manifestations and response to various treatment options of this potentially debilitating disease. The clinical manifestations of the IM in our patient cohort as well as the treatment options and their responses appear to be similar to the other Asian and Western data, including the screening of malignancy and CTD in all IM patients and the use of CS as first line therapy. Screening for malignancies is, therefore, an important part of the management.

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REFERENCES