Clinically Amyopathic Dermatomyositis: Case Report and Review of the Literature

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Abstract—Clinically amyopathic dermatomyositis (CADM) is an autoimmune disease characterized by the presence of skin lesions typical of dermatomyositis and absent/low muscle involvement. One case of hypomyopathic dermatomyositis with early rapidly progressive interstitial lung disease in a 52-year-old woman with fever, erythematous desquamating skin rash, arthralgia and pulmonary consolidation is here reported. The rapid progressive interstitial lung disease caused the patient's death, despite immunosuppressive treatment.

Index Terms—Autoantibodies, Clinically amyopathic dermatomyositis, Immunosuppressive Treatment, Interstitial Lung Disease.

I. INTRODUCTION

Amyopathic dermatomyositis (ADM) is a subset of dermatomyositis (DM) characterized by biopsy-confirmed typical cutaneous manifestations of classic DM occurring for 6 months or longer, with no clinical evidence of muscle weakness and no serum muscle enzyme abnormalities [1-4]. Hypomyopathic dermatomyositis (HDM) is a subset of DM characterized by DM-specific skin disease and no clinical evidence of muscle disease but subclinical signs of myositis on laboratory, electrophysiologic, and/or radiologic evaluation [2]. Both subsets are defined as Clinically Amyopathic Dermatomyositis (CADM), to emphasize their predominantly cutaneous clinical involvement [3]. Several studies have demonstrated that rapidly progressive interstitial lung disease (ILD), with a poor prognosis, can occur in patients with CADM [5-7].

A fatal case of HDM with acute interstitial pneumonia, with a picture of diffuse alveolar damage (DAD pattern) is here reported.

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II. CASE REPORT

A 52-year-old previously healthy Italian woman, with a one-month history of fever, erythematous, desquamating skin lesions, mild anti-nuclear antibody (ANA) positivity and pulmonary consolidation, was admitted to Immuno-Rheumatology Division, S. Andrea University Hospital, Sapienza, University of Rome. Diagnosis of bacterial pneumonia was hypothesized, despite symptom and radiologic abnormality worsening during a one-week oral antibiotic therapy with levofloxacin a few days before hospital admission.

The patient presented fever (T max 39°C), mechanic’s hands, slight heliotropic periobital rash, erythematous elbows, desquamating papules and arthralgias on admission. She did not complain of myalgias, muscle weakness or dyspnea, but only mild dysphagia. At physical chest examination fine bibal crackles were present.

Laboratory results showed red blood cell count 3,300,000/µL; haemoglobin 9.2 g/dl; haematocrit 38%; white blood cell count 2,900/µl (neutrophils 60%; lymphocytes 24%; monocytes 14%); platelet count 110,000/µl; Erythrocyte sedimentation rate (ESR) 56 mm/h; C-reactive protein (CRP) 0.78 mg/dl; aspartate aminotransferase 138 IU/L; alanine aminotransferase 122 IU/L; creatine kinase 113 IU/L; myoglobin 90 IU/L; lactate dehydrogenase (LDH) 1987 IU/L; albumin 2.5 g/dl; C3 106 mg/dl and C4 34.3 mg/dl. Several blood cultures were negative.

ANA, speckled pattern, were detected at 1:80 titre, while extractable nuclear antigens (ENA), including anti-Jo1 antibody, anti-cardiolipin, anti-β2glycoprotein GPI, direct and indirect Coombs and Dixon tests were negative.

Total lymphocytes were 645/µl, CD3+ 385/µl (60%), CD4+ 251/µl (41%), CD8+ 113/µl (18%), CD19+ 151/µl (22%); CD4/CD8 ratio 2.21.

Hand cutaneous biopsy showed a perivascular infiltration, as in microangiopathic vasculitis; immunofluorescence did not show IgG, IgA, IgM, C3 or C4 deposits.

Chest X-Ray showed mild consolidation in left lower lobe and bilateral pleural effusion. Intravenous antibiotic therapy, with amikacin and cefotaxime, was started, without improvement.

After one week, a chest high resolution computed tomographic (HRCT) scan showed diffuse bilateral lung consolidations with bronchogram, and focal ground glass areas with predominantly subpleural distribution, bronchovascular thickening and bibal bronchietasis.
Arterial blood gas analysis, at room air, showed pH 7.52, pO2 53 mmHg, pCO2 41 mmHg, SpO2 89.9%. Therefore, the patient was treated with oxygen therapy (6 L/min) and cefotaxime was stopped and meropenem and teicoplanin were started.

Fibrobronchoscopy was performed in order to collect bronchoalveolar lavage (BAL) fluid, which contained 240,000 cells/ml, with 67% macrophages, 29% lymphocytes (CD4+ 32%, CD8+ 52%, CD19+ 0%) and 4% neutrophils; CD4/CD8 ratio 0.6. A mild restrictive pattern appeared at pulmonary function tests (PFT).

Therefore, methylprednisolone 80 mg/day was started. However, her clinical condition deteriorated; fever persisted, dry cough, tachypnea and tachycardia occurred, and abnormalities in muscle enzyme levels were detected. Chest X-Ray and HRCT were repeated and documented a severe deterioration, characterized by acute interstitial pneumonia with rapid fibrotic evolution. (Fig. 1.)

On the fourth day pulse methylprednisolone (1 gr/die for 3 days) was thus instituted, without any improvement. Atrial fibrillation appeared and was treated with intravenous propafenone; then severe respiratory failure occurred, so the patient was admitted to intensive care unit where non-invasive ventilation (NIV) was started. Vital signs taken at that time revealed a blood pressure of 80/45, temperature of 38.4°C, pulse rate of 110 beats/min, irregular, with electrocardiographic characteristics of recurrent atrial fibrillation. The patient died four days later.

The autopsy showed DAD, including oedema and hyaline membranes, diffuse ischemic myocardial damage and centrilobular hepatic necrosis were detected. There were no pathological muscle findings at histology and fibrinoid necrosis of the small vessels was found in deep dermis.

III. DISCUSSION

DM is a connective tissue disorder characterized by skin and muscle inflammation [8].

In 1979 Pearson described several cases of ADM, a rare form of DM characterized by the classic cutaneous lesions, persistent for more than 6 months to 2 years, without muscle involvement [2]. There is a subset of patients who have typical DM skin lesions, but only subclinical myopathy which is called HDM. Sontheimer defined these two conditions CADM [3] and established four diagnostic criteria for amyopathic dermatomyositis: 1) cutaneous changes pathognomonic for DM; 2) skin biopsy findings indicative of DM; 3) no clinical evidence of muscular weakness within 2 years of skin disease onset; 4) normal serum muscle enzyme level for 2 years after the development of skin lesions [1]. Subsequently the interval for CADM diagnosis has been reduced from 2 years to 6 months [9].

It has been estimated that about 10% to 20% of DM patients seen in dermatology department have a CADM. The epidemiology of CADM has not been well characterized. However, a systematic review by Gerami et al. [10] analyzed the published literature on adult-onset CADM until May 2004 and identified 291 adult-onset CADM cases (18 years or older) reported from over 19 Countries; 36/291 (13%) of the identified published CADM patients developed ILD and in 173 cases the patients’ race was reported, 121 being Caucasian (70%), 23 Chinese (13%), 23 (13%) Japanese, 3 (2%) Korean, 1 (<1%) African American, 1 (<1%) Mexican, and 1 (<1%) West Indian. Table 1 report an update of cases until March 2013.

<table>
<thead>
<tr>
<th>Country</th>
<th>No. of cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>USA</td>
<td>73</td>
</tr>
<tr>
<td>Germany</td>
<td>39</td>
</tr>
<tr>
<td>Japan</td>
<td>37</td>
</tr>
<tr>
<td>Taiwan</td>
<td>23</td>
</tr>
<tr>
<td>Hong Kong</td>
<td>17</td>
</tr>
</tbody>
</table>
Further epidemiological studies show that the prevalence of ILD in CADM patients is 29% in Americans [11] whereas in Asians is relatively higher [12, 13]. These data may suggest racial differences in the susceptibility of ILD in CADM patients.

There is a female-to-male predominance of approximately 3:1 in CADM. The age of onset is typically in the fifth decade. The histological features of skin involvement in CADM and DM are indistinguishable; both are characterized by a vacuolar interface dermatitis with mucin deposition in dermis and inflammatory infiltrate.

ILD is a common complication of DM/polymyositis (PM), with an estimated incidence ranging from 20% to 65% [14]. Several studies have shown the poorer prognosis of DM-ILD in comparison with PM-ILD. Moreover, DM-ILD is more refractory to corticosteroid therapy and requires more often an additional immunosuppressive treatment [15].

Prevalence of ILD in CADM ranges from 0% to 83.3%, with a high frequency of rapid progressive interstitial lung involvement. Rapid progressive lung disease is defined when the respiratory failure develops within 3 month from the onset of pulmonary symptoms [16].

ILD-CADM includes two different form, acute/subacute and chronic, each with distinct features and prognosis. Acute/subacute form, which represents 2/3 of ILD-CADM is developing a severe respiratory failure [17]. Chronic ILD, differently, has a mild course and a good response to steroid therapy [18]. Several studies have demonstrated that in all patients with acute/subacute form, ILD simultaneously occurs with CADM, meanwhile more than half patients with the chronic form develop ILD after the CADM diagnosis [19].

The mortality between the two forms is very different; patients with acute/subacute ILD-ADM have a much lower survival rate than those with chronic ILD-ADM (5-yr survival 35% versus 100%, respectively) [17].

In acute/subacute ILD systemic symptoms, including fever and arthralgias, are more frequent. It has been demonstrated that patients with lower arterial pO2, higher LDH value and arthralgias/arthritis have a poor prognosis as reported in Table 2 by Ye et al. [20], also confirmed by clinical features of this case report.

<table>
<thead>
<tr>
<th>Case</th>
<th>CADM-ILD (Deceased) n = 12</th>
<th>CADM-ILD (Survived) n = 9</th>
<th>Case Report</th>
</tr>
</thead>
<tbody>
<tr>
<td>PO2 mmHg</td>
<td>56±17*</td>
<td>77±19</td>
<td>53</td>
</tr>
<tr>
<td>LDH (normal &lt;220 IU/L)</td>
<td>459±120**</td>
<td>303±96</td>
<td>1987</td>
</tr>
<tr>
<td>ANA titre &gt; 1:80</td>
<td>1/11*</td>
<td>4/8</td>
<td>1:80</td>
</tr>
<tr>
<td>Arthritis or arthralgia</td>
<td>8*</td>
<td>1</td>
<td>+</td>
</tr>
</tbody>
</table>

*p < 0.05  **p < 0.01

Table 2. Clinical features of CADM-ILD

Moreover, hypoalbuminemia and high ESR value are additional risk factors and may reflect patient’s poor general status, conversely high titre positive ANA seem to be protective and it has been postulated that patients with CADM-ILD and a history of disease longer than 24 months have a good prognosis [21].

Autoantibodies to specific nuclear or cytoplasmic antigens occur in about 60-80% of patients with PM/DM. Myositis autoantibodies have been divided into myositis-specific autoantibodies (MSA), that occur exclusively in patients with myositis, and myositis-associated autoantibodies (MAA), that can also develop in patients with secondary myositis or connective tissue diseases without myositis [22]. They are usually present from the early stages of disease and persist over time even when disease is controlled, although the titre may change or occasionally become negative. The only MSA antibody identified by common diagnostic techniques is anti-Jo1, which is present in approximately 20% of patients with myositis. The other MSA antibodies are instead less frequent (1-3%).

The presence of an autoantibody strongly associated with CADM and rapidly progressive ILD has recently been reported, and this antibody was named “anti-CADM-140 antibody” [23]. Sato et al. have found the presence of anti-CADM-140 antibody in 27 of 32 patients with CADM and in 1 of 294 patients with various connective tissue diseases or idiopathic pulmonary fibrosis. This protein was identified with an RNA helicase encoded by melanoma differentiation-associated gene 5 (MDA-5) [24]. RNA helicase encoded by MDA-5 is implicated in innate immune defence against viruses, cellular growth suppression and apoptosis. In particular, it has been shown that RNA helicase is essential for the production of interferon in response to picornavirus RNA; interferon is critical to suppress viral replication and modulate the subsequent adaptive immunity [25]. Therefore, it has been hypothesized that a
picornavirus infection may play an important role in the pathogenesis of CADM and rapidly progressive ILD. Detection of anti-CADM-140 antibodies can be done by immunoprecipitation assay (gold standard) or by enzyme-linked immunosorbent assay (ELISA), using recombinant MDA-5 protein as antigen. This technique has an analytical specificity of 100% and an analytical sensitivity of 85% in comparison with immunoprecipitation assay.

A newly recognized autoantibody, anti-p155, is associated with DM, cancer-associated DM (75%) and recently it has also been associated to ADM [26].

Radiologic findings of PM/DM-associated ILD have been extensively reported [14, 27]. The most commonly detected abnormalities are ground-glass opacity, consolidation, septal lines, traction bronchiectasis, reticulation, subpleural lines, parenchymal bands, honeycombing, micronodules, cysts. These pathologic patterns are localized primarily at the lung bases and subpleural areas bilaterally [28].

Most ILD show a common pattern in PFT, which is represented by a restrictive ventilatory defect and reduced diffusing capacity lung carbon monoxide (DLCO), Pulmonary function tests, forced vital capacity (FVC), and DLCO in particular, are important predictive factors for survival of clinical ILD [6].

PFT can aid in diagnosis (although the pattern of abnormality is nonspecific) and establishing disease severity, therefore this examination can define prognosis and monitor response to therapy and disease progression [29]. In patients with rapidly progressive ILD, in addition to increased creatin-phospho-kinase (CPK) and CRP levels, highest values of pH arterial and lower PaO2/FiO2 than patients with ILD slowly progressive [30] have been found.

Established treatments for CADM-ILD do not exist yet and this poses a critical problem. Chronic ILD shows a mild course and responds well to corticosteroids; however, patients with acute/subacute ILD do not respond to corticosteroids alone and need additional immunosuppressive agents [31].

An optimal immunosuppressive agent has not yet been established, even though in the literature case series and case reports, showing the efficacy of different immunosuppressive drugs, such as azathioprine [32], cyclosporine, mycophenolate [33] and cyclophosphamide, are present.

Some studies recommend the use of cyclosporine and/or cyclophosphamide in the early phase of disease [15, 34-35].

IV. CONCLUSION
A case of HDM with early severe pulmonary involvement and late muscular symptoms accompanied by mild increment of muscular enzymes is here reported.

The diagnosis is in agreement with literature reports of cases of amyopathic/hypomyopathic DM with rapidly progressive interstitial lung disease characterized by low titre positive ANA, hypoaalbuminemia and late/absent increase of muscular enzymes.

It was not possible to evaluate the positivity of newly recognized autoantibodies for the reduced availability of laboratories able to detect the whole spectrum of antibodies specific for CADM. This problem and the predominant pulmonary involvement, initially not accompanied by signs of myositis, initially attributed to a concomitant infection, has further hindered an early diagnosis in our patient.

This case underlines the diagnostic difficulty of ILD-CADM, particularly in presence of such a rapid and aggressive course that the patient dead in 4 weeks, rarely reported in the literature among Caucasian patients.

REFERENCES


