Fatal outcome in a case of dermatomyositis and Hamman-Rich syndrome

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ABSTRACT

We present the fatal outcome in a 31-year-old woman of Latin-American origin diagnosed with dermatomyositis. There were three months between death and the onset of symptoms. The initial presentation was normal dermatological symptoms to which were shortly added clinical signs of effects on the lungs, as was shown radiologically and through pulmonary function tests which were subsequently identified histologically as Hamman-Rich syndrome. The patient was treated with high doses of corticosteroids, intravenous (IV) immunoglobulin, cyclophosphamide and cyclosporin. We carried out a review of the literature on pulmonary compromise in dermatomyositis, clinical and anatomopathological forms and treatment alternatives.

Keywords: Interstitial lung disease; Dermatomyositis; Hamman Rich Syndrome

CASE DESCRIPTION

A 31-year-old woman of Latin-American origin with no history of drug abuse and a normal pregnancy 6 years earlier was sent to our department from the emergency unit due to dyspnoea.

Seven weeks earlier she had presented with erythematous, desquamative lesions distributed in the form of plaques with ill-defined edges on both eyelids, the forehead, breasts, periumbilical region, buttocks, metacarpophalangeal joints of the fingers and the dorsal cervical region. A skin biopsy showed a chronic perivascular and periadnexal infiltration with accumulation of histiocytes in the papillary dermis and mucin deposits in the reticular dermis. From these findings she was diagnosed with amyotrophic dermatomyositis at another centre and treatment was initiated with oral prednisone (0.5 mg/kg/day) and topical betamethasone.

After six weeks with no improvement and the appearance of fever, weakness and general malaise, she was hospitalised for administration of IV methylprednisolone at a dose of 40 mg/day (body weight 50 kg). The patient's skin lesions did not improve, while there was mild improvement in the asthenia and general weakness. Lab tests showed AST 707 U/L, ALT 802 U/L, total bilirubin 0.52 mg/dL. GGT 311 U/L, ALP 240 U/L, LDH 830 U/L. Erythrocyte sedimentation rate (ESR) was 33 mm/h (range 0-20), C-reactive protein (CRP) 0.9mg/L (range 0-5), ferritin 2141 ng/L and procalcitonin 0.40 ng/mL. Aldolase was 10.10 U/L (range 0--2.5), CK 170 U/L (range 26-140). The lipid and thyroid profile and the white cell count (CBC) were normal. The aRo, aLa, ANA, dsDNA, MI2, SRP, PM-SCL, PL7, PL12, KU, OJ, EJ immunological profile and antiphospholipid antibodies were negative. Viral and autoimmune hepatitis were ruled out. A deltoid biopsy showed inflammatory areas with the presence of mononuclear cells around the permysium with perivascular deposits.

The body CT scan showed interstitial ground-glass opacity in the pulmonary parenchyma in the bases and inferior lobes with peripheral distribution (Figure 1 A), but no other notable findings in other organs.

With the diagnosis of dermatomyositis affecting the skin, muscle, lung and liver, the patient was discharged with 50 mg/day of oral prednisolone.

A week later she presented in the ER with moderate effort dyspnea and tachypnea, that was our first contact with her and was hospitalized in our beds. She had baseline peripheral oxygen saturation of 91% with good response to oxygen supplementation. There was wheezing in both lung bases and residual skin lesions. Laboratory tests showed: Aldolase 2.94 U/L, CK 28 U/L, AMA 1/160, CRP 9.86 mg/L, ESR 52mm/h and CBC with 900 lymphocytes.

A further thoracic CT showed important progres-

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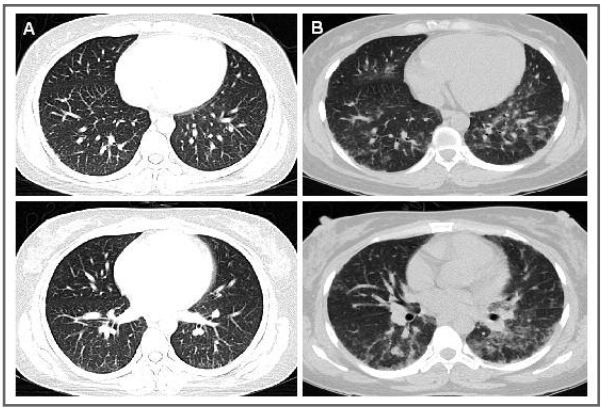

FIGURE 1. Radiological evolution of lung CT scan. **(A)** At the time of diagnosis, CT scan showed interstitial ground-glass opacity in the bases and inferior lobes with peripheral distribution. **(B)** 25 days later, CT scan images demonstrated an important progression of the lung lesions and areas of fibrosis and honeycomb in both lung bases

sion of the lung lesions since the previous CT (25 days earlier, see B of Figure 1), with ground-glass opacity at both apices and areas of fibrosis and honeycomb in both lung bases.

Pulmonary function tests showed a drop in FVC (53.8%), DLCO and 6MT with significant desaturation from the start of the test. Her echocardiogram was normal.

During hospitalisation, the prednisolone dose was increased to 1.5 mg/kg/day due to rapid functional and radiological deterioration. On the third day of treatment, the dyspnoea worsened and was accompanied by fever, so immunoglobulins were added (Flebogamma® 1g/Kg/d, two days, 60g/d). At that time, the tests showed an increase in CRP (33.10 mg/L), ESR (74 m/h), CBC with leukocytosis of 26,700/uL with a predominance of neutrophils, lymphopaenia of 100/uL and normochromic and normocytic anaemia (haemoglobin of 7.5 g/dL) with no clinical signs of active bleeding.

Six days later, the patient was admitted to the ICU, requiring non-invasive mechanical ventilation. Three pulses of methylprednisolone (together with prednisone 1 mg/kg/d) and one 750-mg pulse of cyclophosphamide were administered. Although there was no sign of associated bacterial or fungal infection, meropenem, vancomycin and amphotericin B were administered. Two days later the patient required mechanical ventilation and inhaled nitric oxide was administered. It was decided to administer cyclosporine by nasogastric tube at 3 mg/kg/d (150 mg/d) and extracorporeal membrane oxygenation (ECMO) was initiated.

There was consultation regarding the possibility of a lung transplantation, but this was ruled out due to the patient's acute condition.

After six days with ECMO, the patient suffered cardiac arrest and died. The necropsy showed diffuse alveolar damage with type II pneumocyte hyperplasia, foci of alveolar haemorrhage and complete absence of signs of infection.

DISCUSSION

CLINICAL-PATHOLOGICAL CLASSIFICATION

In accordance with exclusively clinical criteria and based on the initial presentation and its severity, pulmonary interstitial disease in patients with dermatomyositis may be classified in three groups: acute, progressive and asymptomatic disease[1].

The acute form, known as acute interstitial pneumonia (AIP) is synonymous for Hamman-Rich syndrome[1,2]. Hamman-Rich syndrome progresses with a histological form known as diffuse alveolar damage (DAD) and is practically indistinguishable from that which appears with adult respiratory distress syndrome. There are two presentations of DAD: exudative or acute and subacute. The exudative presentation is the earliest. It appears in the first week and is characterised by intra-alveolar oedema, the presence of hyaline membranes and type II pneumocyte hyperplasia, intra-alveolar haemorrhage and interstitial infiltration of mononuclear inflammatory cells. Subsequently, two weeks after the lesion, a second phase appears, known as the proliferative phase, characterised by a massive fibroblastic proliferation in the interstitial tissues and the alveolar space. Hyperplasia of the type II pneumocytes is also observed, with a discrete degree of nuclear atypicality, thrombosis of the small arteries and squamous metaplasia in the bronchial epithelium[2].

Subacute DAD, known also as the progressive DAD, corresponds to subacute interstitial pneumonia (SAIP). The difference between AIP and SAIP is in the onset of symptoms. While AIP appears in the first month, SAIP may appear between the first and third months[3].

SAIP also has three different histological forms: bronchiolitis obliterans organising pneumonia (BOOP), usual interstitial pneumonia (UIP) and non-specific interstitial pneumonia (NSIP). The NSIP form is histologically very similar to the acute form of DAD

except for the presence of large amounts of collagen in the fibrotic areas. BOOP also has similar histological characteristics to acute DAD except it is mainly patchy and affecting the peribronchiolar area in particular. UIP is characterised by a fibrotic and homogenous pattern that does not vary with time. This pattern may be observed in patients who have received mechanical ventilation with high concentrations of oxygen[2]. Special mention should be made of the fact that cryptogenic organising pneumonia (COP) is normally an interchangeable term for BOOP[4]. COP certainly refers to histological patterns of BOOP in which a known underlying pathology has not been identified.

The third group of patients, estimated as 22 to 25% of all cases of PM/DM, is made up of asymptomatic patients with respect to respiratory function who have typical radiological findings: parenchymatous micromodules, linear opacities, irregularities in the pleura-lung interface, ground-glass opacity, honeycomb patterns, bronchiectasis and bronchioloectasia[1,5].

TREATMENT ALTERNATIVES

Interstitial lung disease in patients the dermatomyositis (DM/ILD) has a poor prognosis in itself. Furthermore, DAD worsens the prognosis. It is normal to observe lower CK levels in patients with DM/ILD compared to patients with PM/ILD and levels may even be normal in patients with DM/ILD. According to some authors, low CK levels are factors for poor prognosis and bad response to corticosteroids in ILD[6]. According to Nawata *et al*[7], the use of prednisolone pulses is still the first line of treatment in ILD and is the most frequently observed recommendation. Although most patients in their series responded well to pulses, only one of them was diagnosed with DM. Currently, therapy with corticosteroids alone, in pulses or not, appears to have more chance of success in patients with PM/ILD in histological forms compatible with BOOP or NSIP, and in clinical forms of ILD corresponding to AIP[1,8].

Also, two studies support the use of cyclosporine A (CYP-A) in patients diagnosed with DM/ILD and AIP. Kameda *et al*[8] published a series of over 500 patients diagnosed with DM, 27 of whom developed ILD and were treated with 0.5 mg/kg/day of prednisolone, 10--30 mg/kg of CYC IV every 3-4 weeks and 2-4 mg/kg/d of CYP-A. According to their findings, survival increased to 50%. The most recent work supporting the use of CYP-A was published by Kotani *et al*[9] in 2011. With a dose of 4 mg/kg/d of CYP-A and 1 mg/kg/d of prednisolone, they reported an improvement in pulmonary function tests and radiological findings and one case of mortality in 14 patients who were followed.

Therapy with rituximab (RTX) has been considered in patients with DM/ILD having previously failed with corticosteroids and other conventional therapies. Despite the lack of case reports, the results appear to be optimistic in the medium term[10,11]; however there are no positive results in situations of rapid progression. The use of anti-CD20 therapy has been reported in patients with ILD and antisynthetase syndrome. The longest series was published by Sem *et al*. They reported 11 cases of antisynthetase syndrome and ILD. Three of them showed rapid deterioration of respiratory function and were treated with RTX before cyclophosphamide, obtaining improvement in DLCO of at least 15%. In 65% of all patients, a minimum of 10% gain in pulmonary vital capacity was observed that was only demonstrable in the first month of treatment[12].

The case we present is a rapidly developing DM/ILD, with low CK levels, compatible with an AIP and histologically corresponding to Hamman-Rich syndrome. Given the rapid deterioration in lung function, an infectious process was suspected, hence empirical antibiotic treatment was administered together with immunosuppressant therapy. Particularly striking was the lack of response to all treatment strategies: use of corticosteroids at high doses and in IV pulses, immunoglobulins, cyclophosphamide and cyclosporin A. The use of RTX was not considered in this patient due to the lack of a short-term favourable response. One day before death, the possibility of lung transplantation was considered, but this was ruled out due to the patient's acute condition.

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