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MI-11. FAVORABLE RESPONSE TO IMMUNOSUPPRESSIVE THERAPY IN A PATIENT WITH ANTI-MDA5 POSITIVE DERMATOMYOSITIS AND RAPIDLY PROGRESSIVE INTERSTITIAL LUNG DISEASE.

(Respuesta favorable a la terapia inmunosupresora en un paciente con dermatomiositis ANTI-MDA5 positiva y enfermedad pulmonar intersticial rápidamente progresiva).

Daniel S. Ulloa-Ruiz [1]
Karina F. Pucha-Aguinsaca [2]
Octavio J. Salgado [3]
Lucía E. Beltrán-Segovia [4]
Lizette Espinosa-Martin [3]

[1] School of Medicine, Universidad Católica de Cuenca (UCACUE), Cuenca, Ecuador.
[2] Chair of Rheumatology, School of Medicine, Universidad Católica de Cuenca (UCACUE), Cuenca, Ecuador.
[3] Department of Medical Investigation, School of Medicine, Universidad Católica de Cuenca (UCACUE), Cuenca Ecuador.
[4] Department of Internal Medicine, Hospital Aída León de Rodríguez Lara, Girón, Azuay, Ecuador.
octavio.salgado@ucacue.edu.ec

Abstract

Anti-MDA5 dermatomyositis (DM) is a subgroup of autoimmune myopathies whose prevalence ranges from 0.55 to 6 cases per 100,000 populations. This condition is frequently associated with rapidly progressive interstitial lung disease, leading to increased morbimortality. The therapeutic approach to anti-MDA5 DM is currently challenging due to its heterogeneous clinical presentation and lack of a standardized treatment. Case presentation: A 49-year-old male patient attended a health center complaining about proximal muscle weakness, weight loss, cough, dyspnea on moderate

to low exertion and a cutaneous rash. He had a family history of rheumatoid arthritis and hypothyroidismus. Laboratory findings showed moderate leukopenia, CK, LDH and Aldolase A in normal range. Ferritemia extremely elevated. Rheumatic tests were negative. The autoantibody screening panel for inflammatory myopathies showed positivity for anti-MDA5. As an anatomical correlate of the latter finding, a reticular interstitial pattern with bibasal predominance was found both in the chest x-ray and in the pulmonary CT. A diagnosis of Dermatomyositis associated with a rapidly progressive interstitial lung disease was made, and immunosuppressive therapy with high doses of glucocorticoids and azathioprine was started. A significant improvement of muscle weakness and skin lesions was seen in response to immunosuppressive therapy. There was also improvement of lung function parameters. After 26 months of treatment, the patient was swichted to mycophenolate mofetil, because o due to slighty decreased FEV1 on a control spirometry and alterations in stress blood gases. The present case illustrates the current limitations in treating the rapidly progressive interstitial pneumopathy which usually appears in association with anti-MDA5 positive dermatomyositis.

Keywords: Dermatomyositis, Interstitial Lung disease, Immunosuppresion, Spirometry.

Resumen

La dermatomiositis (DM) anti-MDA5 es un subgrupo de miopatías autoinmunes cuya prevalencia oscila entre 0,55 y 6 casos por 100.000 habitantes. El abordaje terapéutico de la DM anti-MDA5 es actualmente un reto debido a su presentación clínica heterogénea y a la falta de un tratamiento estandarizado. Presentación del caso: Un paciente varón de 49 años acudió a un centro de salud quejándose de debilidad muscular proximal, pérdida de peso, tos, disnea de moderados a leves esfuerzos y erupción cutánea. Tenía antecedentes familiares de artritis reumatoide e hipotiroidismo. Los resultados de laboratorio mostraron leucopenia moderada, CK, LDH y Aldolasa A en rango normal. Ferritemia extremadamente elevada. Las pruebas reumáticas fueron negativas. El panel de detección de autoanticuerpos para miopatías inflamatorias mostró positividad para anti-MDA5. Como correlato anatómico de este último hallazgo, se encontró un patrón intersticial reticular de predominio bibasal tanto en la radiografía de tórax como en el TAC pulmonar. Se realizó el diagnóstico de Dermatomiositis asociada a una enfermedad pulmonar intersticial rápidamente progresiva y se inició tratamiento inmunosupresor con altas dosis de glucocorticoides y azatioprina. Se observó una mejoría significativa de la debilidad muscular y de las lesiones cutáneas en respuesta al tratamiento inmunosupresor. También mejoraron los parámetros de la función pulmonar. Tras 26 meses de tratamiento, el paciente fue cambiado a micofenolato mofetilo, debido a una ligera disminución del FEV1 en una espirometría de control y a alteraciones en la gasometría de esfuerzo. El presente caso ilustra las limitaciones actuales en el tratamiento de la neumopatía intersticial rápidamente progresiva que suele aparecer asociada a la dermatomiositis anti-MDA5 positiva.

Palabras clave: Dermatomiositis, enfermedad pulmonar intersticial, inmunosupresión, espirometría.

INTRODUCTION

Idiopathic inflammatory myopathies (IIM) are a group of heterogeneous diseases whose common manifestations are muscle weakness and inflammation (1). According to the EULAR (European Alliance of Association for Rheumatology)/ACR (American College of Rheumatologists) classification (2), patients meeting > 55% of the criteria for IIMs can be further subclassified, according to the age of onset of first symptoms,

into adult (age > 18 years) or juvenile (age < 18 years) forms.The adult forms of IIM are: (a) Polymyositis (PM), which includes the inmuno-mediated necrotizing myositis (IMNM) (b) inclusión-body myositis (IBM) (c) Clinically amyopathic dermatomyositis (CADM), (d) Dermatomyositis (DM) and (3) Overlap myositis (3).

A detailed description of each of the clinical variants of IIM would be beyond the scope of the present work. Moreover, each of the variants has a very different course and prognosis. However, it is important to note that patients with PM, CADM and DM in up to 40% of cases may have associated interstitial lung disease (ILD), which is one of the most severe extramuscular manifestations of IIM and severely affects the patient's quality of life and survival (4).

It has been found that CADM-ILD and MD-IL are much more refractory to treatment than PM-ILD (5). Lung involvement may be acute (rapidly progressive interstitial lung disease, RP-ILD) or subacute progressive when worsening of ILD occurs within 3 months. In contrast, chronic forms of ILD are characterized by a gradual progression of lung lesions over a period > 3 months (slowly progressive ILD) or, very rarely, absence of deterioration over the same period (stable ILD) (2). A fundamental aspect of the diagnosis of ILD is the presence of certain myositis-specific autoantibodies (MSA) (6). The presence of MSA such as anti-aminoacyl tRNA synthase antibody (ARS) as well as anti-melanoma differentiation-associated gene 5 antibody (anti-MAD5) is closely linked to the presence of an underlying ILD (7). The anti-ARS antibodies are actually a group of 8 antibodies (Jo-1, PL-7, PL-12, EJ, OJ, KS, Zo, and Ha) and their positivity may indicate the presence of an anti-synthetase syndrome whose clinical phenotype and response to treatment differs from that of anti-MAD5 positive DM or CADM (8). Anti-MAD5 positivity is associated with a high incidence of concomitant ILD, especially RP-ILD in which there is a refractory response to treatment and a poor prognosis (9,10). There are no prospective studies that support a standardized therapeutic approach to these cases and the evidence available comes from non-randomized retrospective observational studies and case series (11). The present work describes a documented case of anti-MAD5 positive DM associated with RP-ILD (Anti-MAD5+ DM/RP-ILD). The results of immunosupressive therapy in this case are described.

Case presentation

The patient is 49 years old, male, sportsman, with no relevant personal pathological history, who, in June 2020, following a upper respiratory viral disease complicated by severe otitis, initiated a clinical picture characterized by progressive muscle weakness affecting mainly the muscles of the neck, shoulder, hips and thighs, accompanied by muscle pain, asthenia, easy fatigability and non-productive cough. In the subsequent 2-3 weeks, profuse night sweats, persistent insomnia, febricula and a transient 2-week lasting skin rash on the knuckles and elbows added to the picture (Fig. 1). In addition, the cough became productive and there was increasing dyspnea with a SAT of 76%. Along with this, the muscle weakness worsened to the point of limiting his ability to ambulate unassisted or even to do his personal care. In July 2020, the patients was evaluated by an internist. On physical examination, the patient was in regular condition, tachypneic. There was a notorious symmetrical muscle weakness at proximal level, with muscle strength of 1/5 in proximal muscle groups (according to the Medical Research Council scale). Bilateral crepitant rales were auscultated on the basal lung fields. Bilateral violaceous scaly patches on metacarpophalangeal and proximal interphalangeal joints (Gottron papules) were observed (Fig. 1). There was pain on palpation in the proximal muscles of the four limbs. Blood samples

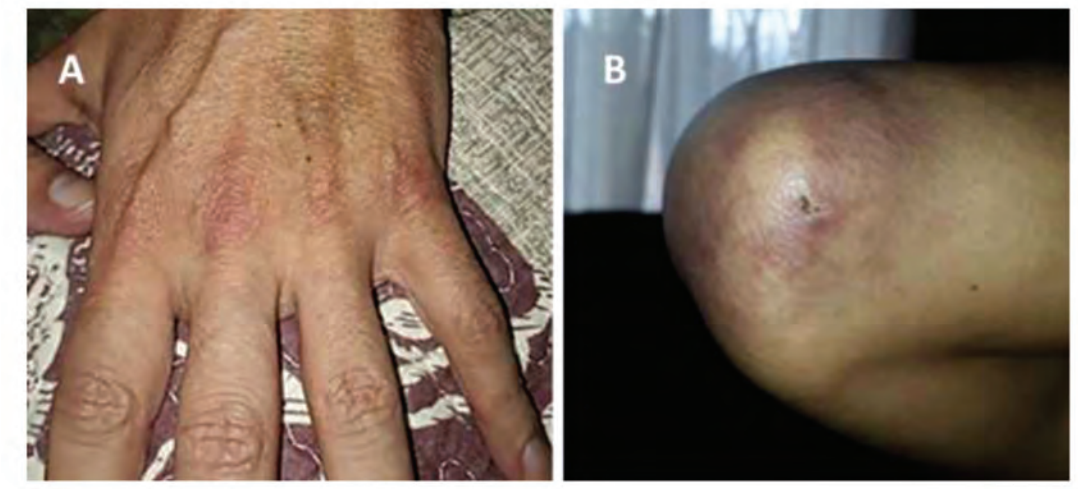

Fig. 1. A. Transient skin lesions in metacarpal region and elbows that lasted 2 weeks and disappeared spontaneously. B. Violaceous scaly patches on metacarpophalangeal and proximal interphalangeal joints (Gottron papules) can be observed.

were taken for rheumatic disease screening because some of the patient's closest relatives, including his mother and his sister, suffered from rheumatoid arthritis. His sister had also had an episode of pulmonary tuberculosis. The patient also stated that his mother and all of his mother's siblings also had hypothyroidism.

Laboratory tests showed Hb of 13.6 mg/dl, mild leukopenia (4,320/mm3) with lymphopenia and eosinopenia, CPK, LDH, Aldolase A, and alkaline phosphatase were within the reference range as well as ALT and CRP. AST 79 IU/L and Gamma GT 311 U/L were slightly elevated. Rheumatoid factor, antinuclear antibodies, and antiDNS were negative. T3, T4, and TSH were normal. Tumor markers were also determined and only CEA was slightly elevated.

Due to worsening respiratory symptoms and altered arterial blood gas profile (PCO2: 34.90 mmHg, PO2 58.60 mmHg, HCO3 24 meq/L), a chest X-ray was performed in August 2020 showing a bilateral diffuse reticular infiltrates with basal predominance and signs of incipient pulmonary fibrosis, without consolidations. The possibility of autoimmune disease was raised due to a family history of rheumatic diseases and hypothyroidism. The patient was admitted for further diagnostic evaluation. The smear microscopy for tuberculosis and sputum cultures were negative. COVID19 test was negative. Arterial blood gases: PCO2 34.90 mmHg, PO2 58.60 mmHg, HCO3 24 meq/L. Samples were taken for rheumatological tests (C-Reactive Protein, Antinuclear Antibodies (ANA), Rheumatoid Factor, Cyclic Citrullinated Peptide, C3, C4, anti-DNA, anti-cardiolipin, anti-LA (SS-B), anti-RO (SS-A) and Anti RNP). Meanwhile, due to a history of previous exposure to TBC at home (sister), the patient initially received anti-TBC treatment despite negative smears. Anti-TBC treatment was discontinued after 2 weeks, as sputum cultures were negative and no improvement was observed. Instead, dexamethasone, antibiotherapy, and salbutamol were administered because of suspicion of underlying immunological disease. With this treatment, substantial improvement in muscle weakness, fever and cough was observed. The results of the aforementioned rheumatologic tests were negative or within normal.

He was discharged at the end of August 2020 without treatment. However, a week later he experienced a severe relapse of symptoms to the point that he was unable to walk or hold his head upright. In September 2020 he was evaluated by a pulmonologist who ordered a pulmonary CT scan that showed a reticular interstitial pattern associated with ground-glass opacification predominantly in the lower lobes and more marked in the right lung than the left (Fig. 2). Bronchoscopy was performed and reported as normal. In parallel, the patient also consulted a rheumatologist who requested a panel of antibodies for myopathies (anti-MDA5, MI-2 alpha, MI-2 beta, TIFIY, NXP2, SAE1, KU, PM-SCL100, PM- SCL75, anti-SSA 52 [RO.52]) and anti-synthetase syndrome (anti-JO-1, SRP, anti-PL-7, anti-PL-12, anti-EJ, anti-OJ). Serum ferritin was found to be 2,551 ng/mL (reference value: < 300 ng/mL in males). While awaiting results, the patient received prednisone (PRED) 100 mg daily and hydroxychloroquine (HCQ), which resulted in dramatic improvement with almost complete remission of muscle weakness, cough and dyspnea. Similarly, oxygen saturation improved substantially to 93%.

When the results of the requested antibody panel were available, positivity only for AntiMDA5 was reported. Anti-MAD5 positive Dermatomyositis associated with rapidly progressive interstitial lung disease (AntiMDA5+ DM/RP-ILD) was diagnosed. Azathioprine (AZA) 50 mg id was added to the treatment and prednisone was gradually weaned down to the baseline dose of 5 mg daily. The patient's condition continued to improve. Spirometry results are shown in Table I. Already in the first spirometry study in November 2020, a restrictive pattern was reported. In November 2022 the improvement has been sustained. Muscle weakness has almost disappeared as well as cough and fever. While the patient so far requires oxygen for heavy exertion, the pulmonary findings have shown no progression. However, at a follow-up consultation with the rheumatologist in November 2022, due to decreased FEV1 on a control spirometry (Table I) and alterations in stress blood gases, AZA was omitted and the patient was switched to Micophenolate Mofetil (MMF) 500 mg bid.

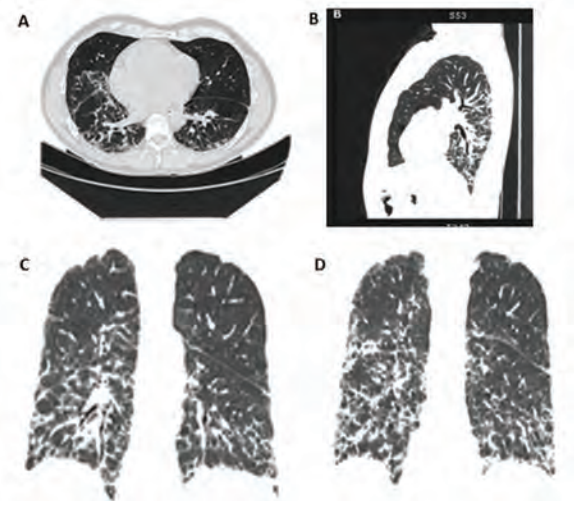

Fig. 2. Thorax CT scan of the studied patient showing reticular interstitial pattern associated with ground-glass opacification predominantly in the lower lobes and more marked in the right lung than the left. A: Axial view B. Sagittal view C. and D: Coronal views.

DISCUSSION

Anti-MDA5+ DM/RP-ILD is a disease that is part of the clinical spectrum of the IIM. Unlike other variants of IIM, it is characterized by the development of RP-ILD with unfavorable prognosis (12). The first cases reported were associated with an amyopathic or hypomyopathic presentation, i.e. no or mild muscle involvement (13). Rams et al. (14) in a study on the clinical features of MIAs concluded that patients presenting with positive anti-MDA5 antibodies were mostly associated with an amyopathic form. However, the degree of muscle involvement is currently under discussion because most studies have evidenced classic presentations with muscle involvement (15), such as the one observed in the present case. Similarly,

Table I
Results of serial spirometric pulmonary function tests in the studied patient under immunosuppresive treatment. FVC: Forced vital capacity. FEV1: Forced expiratory volumen in one second.

Pulmonary Function test	Treatment: PRED 5 mg + AZA 50 mg			Diagnostic Interpretation	
	Spirometry test 1 03/2021	*Spirometry test 2 01/2022*	*Spirometry test 3 09/2022*	*Restrictive pattern*	*Obstructive pattern*
FVC (Normal values: 80%-120%)	68%	77%	75%	< 70%	Normal or slightly decreased
FEV1 (Normal value: 80%-120%)	73%	89%	83%	Normal or increased	< 80%
Tiffeneau Index: FEV1/FVC (Normal Values: 70%-80%)	107%	87%	87%	Normal or increased	<75%

Hall *et al*. (16), in a retrospective study that included 160 patients with IIM, 11 of them presented positive anti-MDA5 and had frank clinical manifestations of myopathy. Cutaneous manifestations vary greatly in this subtype of IIM.

Fiorentino *et al.* (17) in a retrospective study of 77 patients with IIM, identified 10 anti-MDA5 positive patients with Gottron's skin ulcers and papules with typical sites being the lateral nail folds and elbows, and palmar papules. These authors found that this subgroup of patients had an increased risk of arthritis, arthralgia, diffuse hair loss, pain, mouth ulceration and swelling of the hands. Hamaguchi et al. (18) in a multicenter study, reported 43 of 376 patients with DM were anti-MDA5 positive. This subgroup of patients presented with a higher frequency of skin ulcers, which per se were not a prognostic marker. These patients also had a higher frequency of fever and arthritis. Other authors 12 have pointed out that cutaneous manifestations within the spectrum of DM, such as heliotropic exanthema, shawl sign, V sign, mechanic's hands, Gottron's papules, and Gottron's sign have a similar prevalence in patients with anti-MDA5 positive DM compared to anti-MDA5 negative patients. In this regard, our patient had several cutaneous manifestations which as mentioned are common for all types of DM (12).

According to the results of some studies (13,19), in the association of RP-ILD with anti-MDA5 antibody positivity, an influence of the geographic region has been found, since in East Asia and Japan, ILD occurs in 82 to 100% of patients with anti-MDA5 positive DM and the RP-ILD form in 39 to 100% of these cases. In contrast, in Caucasian patients ILD has a prevalence of 38 to 73% and RP-ILD 20 to 57%, i.e. a lower proportion than in Asian patients (17,20). Chen *et al.* (21) in a meta-analysis of anti-MDA5 positive cases and the risk of developing RP-ILD concluded that patients positive for anti-MDA5 antibody are 20 times more likely to develop RP-ILD than those who are negative for this antibody. These authors found that the sensitivity and specificity of the antibody for RP-ILD was 77% and 86%, respectively.

Concerning Latin America, Olivo-Pallo et al. (22) in a cohort study that included health centers in Brazil, Mexico, and Argentina to evaluate the characteristics of patients with anti-MDA5 positive DM found that only 31 (11.4%) of 270 patients with MIA studied presented positivity for anti-MDA5. The prevalence of ILD was 25, 9%, and of RP-ILD 1.5%.

Tanizawa K *et al.* (23) studied the characteristics of ILD seen in lung CT in 25 patients of whom 12 were positive for anti-MDA5 (CADM-140). These authors report that in anti-MDA5 positive patients the ground-glass attenuation pattern was found more frequently, as in the patient of the present case, together with the random consolidation pattern. Furthermore, no intralobular reticular opacities were found in these patients. In contrast, in the negat ive patients, the low reticular pattern was the most common in negative patients.

Hervier and Uzunhan (24), in a review of cases reported in the literature on ILD associated with inflammatory myopathies, found different tomographic patterns of ILD such as (a) organized pneumonia (OP, 50%), characterized by alveolar consolidations; (b) acute interstitial pneumonia (AIP, 30%) in which extensive ground-glass consolidations and opacities are observed; (c) nonspecific interstitial pneumonia (NSIP, 20%), consisting of basal ground-glass opacities and/or linear reticulations; and (d) usual interstitial pneumonia (UIP, 5%), showing basal subpleural reticulations with bronchiectasis and honeycomb lesions. In the case of our patient, a rather mixed pattern was evidenced, with findings typical of NSIP and UP. Interestingly, Allenbach *et al.* (25) describe different clinical phenotypes of anti-MDA5 positive DM. Of 121 cases studied by these authors, 83 were anti-MDA5 positive and of the latter, 18.1%, mostly women, had RP-ILD, mechanistic hands and a high mortality rate. A second group (55.4% of the anti-MDA5 positive cases) had pure rheumatodermatologic symptoms, mostly arthralgias or arthritis, with less frequent RP-ILD and a good prognosis. Finally, the third group (27.5% of the anti-MDA5 positive cases), predominantly men, had severe cutaneous vasculopathy, frequent signs of myositis including proximal weakness, infrequent but with an intermediate prognosis. Our patient fits the criteria of the third group.

The treatment of ILD in DM is currently a therapeutic challenge. Fujisawa (5) in a review of the literature regarding the management of anti-MDA5 positive DM + ILD concludes that although there is currently no standardized treatment for pulmonary manifestations in myositis, glucocorticoids in conjunction with another immunosuppressant are considered the mainstay of treatment. Combinations of steroids with calcineurin inhibitors such as cyclosporine or tacrolimus, with azathioprine, with mycophenolate mofetil, or monoclonal antibodies such as rituximab have been used. Similarly, Romero-Bueno *et al.* (26) after an analysis of the results of 134 studies on the recommendations for the treatment of Anti-MDA5 positive DM + RP-ILD also conclude that, in general, the combined immunosuppressive therapy of high doses of glucocorticoids + calcineurin antagonists with or without cyclophosphamide is the first line treatment.

Tsuji H *et al.* (27), for their part, in line with the results of a prospective multicenter study conclude that initial combined treatment was associated with higher survival rates than that of step therapy in cases of Anti-MDA5 positive DM + RP-ILD. In our case, a favorable outcome was obtained by first using high-dose oral prednisone (40 mg/day), with the subsequent addition of A 50 mg + prednisone at maintenance doses (5 mg/kg). It would be somewhat speculative to assume that if a combination therapy had been administered from the beginning, the results would possibly have been better.

Huapaya JA *et al.* (28) a retrospective study including 66 patients compared the long-term results of combined therapy PRED + AZA vs PRED + MMF in Anti-MDA5+ DM/RP-ILD patients found that PRED + AZA treatment was associated with a significantly greater increase in FVC and CO2 diffusion capacity than in the PRED + MMF group of patients, despite the use of a lower dose of PRED (- 6.6 mg) in the PRED + AZA group. However, it should be noted that adverse effects were more frequent in the AZA group, especially hepatotoxicity. According to the results obtained by Gono et al. (29), in a study with 27 patients with Anti-MDA5+ DM, ferritin and IL-18 levels were higher in patients with PR-ILD than in those without PR-ILD. Thus, they conclude that ferritin levels are very useful to evaluate the pulmonary response to the immunosuppressive treatment applied. On the other hand, Tanizawa et al. (30) evaluated 51 patients with ILD associated with DM and found that the risk factors for 90-day mortality were fever > 38°, ferritin levels greater than 500 ng/ml, positive anti-MDA5 antibodies and presence of ground-glass consolidation image. This agrees with the evaluation made by Gono et al. (29) in their publication in which they evaluate the prognostic factors in 24 patients with Anti-MDA5 positive DM + RP-ILD, concluding that the factor is the ferritin levels since the survival rate was lower in patients with ferritin levels greater than 1600 ng/mL. The patient in the present case had initial ferritin levels of 2,551 ng/ml, which translated into a lower survival. The decrease to normal levels in response to immunosuppressive treatment with PRED + AZA was associated with remission of dermatological and muscular manifestations, and with improvement in respiratory symptoms and, therefore, with better survival.

Summing up, combined therapy with PRED + AZA of Anti-MDA+ DM/RP-ILD administered early in the course of the disease may achieve acceptable results in light of what was observed in the current case and in previous case studies. However, a larger number of cases are needed to consolidate this treatment as first choice option. It remains to be seen in the current case whether swiching to MMF would improve lung functional parameters and patient outcome. The diversity of clinical presentations of Anti-MDA positive DM + RP-ILD will remain a real challenge when deciding on the immunosuppressive scheme to use.

Conflicts of Interest

None

Ethics statements

Written informed consent was obtained from the patient.

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Number ORCID the author

- Daniel S. Ulloa-Ruiz
  0000-0003-3184-9480
- Karina F. Pucha-Aguinsaca
  0000-0003-3188-8527
- Octavio J. Salgado
  0000-0003-2784-5268
- Lucía E. Beltrán-Segovia
  0000-0003-1899-5539
- Lizette Espinosa-Martin
  0000-0002-3455-4437

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MICROBIOLOGÍA (MICROBIOL)

MICROBIOL-01. DETECCIÓN DE CEPAS MULTIRRESISTENTES DE *Staphylococcus aureus* EN LECHE DE VACAS CON MASTITIS CLÍNICA Y SUB-CLÍNICA, EN EL CANTÓN BIBLIÁN, PROVINCIA DE CAÑAR. ECUADOR.

(Detection of multiresistant strains of *Staphylococcus aureus* in milk samples from dairy cows showing clinical and subclinical mastitis in Biblián Canton, Cañar Province. Ecuador).

Mishell Escobar[1]
Arianna Gonzáles[1]
Lenys Buela[2]
Mercy Cuenca-Condoy[3],
María Guamán
Luis Yarzábal[2]

[1] *Estudiante egresado. Carrera de Bioquímica y Farmacia, Unidad Académica de Salud y Bienestar. Universidad Católica de Cuenca. Cuenca - Ecuador.*
[2]*Carrera de Bioquímica y Farmacia, Unidad Académica de Salud y Bienestar. Universidad Católica de Cuenca. Cuenca - Ecuador.*
[3] *Carrera de Veterinaria. Unidad Académica de Ciencias Agropecuarias. Universidad Católica de Cuenca. Cuenca - Ecuador.*
lyarzabalr@ucacue.edu.ec;
yarzabalandres@gmail.com

Resumen

Staphylococcus aureus es una bacteria patógena, causante de infecciones en humanos y animales. Es uno de los agentes etiológicos de la mastitis bovina, infección que puede contaminar la leche, y ser fuente de contaminación para trabajadores y consumidores finales. La presencia de cepas multirresistentes en la leche cruda, representa una amenaza adicional para la salud pública.