A Propos d'un Cas

Diagnostic challenge of anti-MDA5 dermatomyositis with respiratory failure during COVID-19 pandemic: A case report

Défi diagnostique de la dermatomyosite à anti-MDA-5 avec insuffisance respiratoire pendant la pandémie de COVID-19 : A propos d'un cas

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Abstract

Background : Anti-MDA5 antibodies are strongly associated to clinically amyopathic dermatomyositis. Patients frequently develop an interstitial lung disease (ILD) that can lead to respiratory failure. This clinical presentation can be of challenge as it can be confused with that of a viral infection. The poor prognosis makes the early and accurate diagnosis crucial.

Case presentation : Herein, we report the case of a North African patient who experienced a delayed diagnosis and presented with severe hypoxemic respiratory failure. In the context of COVID-19 pandemic, this clinical presentation may pose a problem of differential diagnosis. The patient was given steroid as well as cyclophosphamide pulse therapy with a gradual improvement of the respiratory status.

Conclusions : This case throws light on the importance of testing for anti-MDA5 antibodies in hypomyopathic patients presenting with rapidly progressive ILD.

Keywords : Anti-MDA5 antibody; Dermatomyositis; Interstitial lung disease; Respiratory failure; Case report; COVID-19; SARS-CoV-2.

Résumé

Contexte : Les anticorps anti-MDA5 sont fortement associés à la dermatomyosite amyopathique clinique. Les patients développent fréquemment une pneumopathie interstitielle diffuse (PID) pouvant conduire à une insuffisance respiratoire. Le pronostic sombre rend le diagnostic précoce et précis crucial.

Présentation du cas : Nous présentons le cas d'un patient nord-africain ayant subi un diagnostic retardé et présentant une insuffisance respiratoire hypoxémique sévère. Dans le contexte de la pandémie de COVID-19, cette présentation clinique peut poser un problème de diagnostic différentiel. Le patient a reçu une thérapie par bolus de stéroïdes ainsi que du cyclophosphamide avec une amélioration progressive de l'état respiratoire.

Conclusions : Ce cas met en lumière l'importance du dépistage des anticorps anti-MDA5 chez les patients hypomyopathiques présentant une PID à progression rapide.

Mots-clés : Anticorps anti-MDA5, Dermatomyosite, Pneumopathie interstitielle diffuse, Insuffisance respiratoire.

INTRODUCTION

Dermatomyositis (DM) is an idiopathic inflammatory myopathy that presents with symmetrical proximal muscle weakness, muscle inflammation, interstitial lung disease (ILD) and cutaneous as well as systemic symptoms (1). Clinically amyopathic DM (CADM) is a clinical subtype of DM that is characterized by minor muscle involvement.

Anti-melanoma differentiation-associated gene 5 (MDA5) antibody, previously known as anti-CADM-140 antibody, have been identified in 2005 as associated to CADM (2). Patients with anti-MDA5 antibody-positive DM exhibit a significantly higher risk of developing a rapidly progressive ILD (RP-ILD) thus a poor prognosis (2).

Because of its low prevalence and its peculiar clinical presentation, it can be challenging to diagnose CADM. Patient can present with acute respiratory failure and systemic symptoms in the foreground with a predominance of extra muscular manifestations, a clinical presentation that would first suggest viral infectious causes, particularly in an evocative epidemiological context. This would make it even more difficult to recall the rare diagnosis of CADM.

Herein, we report a case of anti-MDA5 antibody-positive hypomyopathic DM complicated with severe ILD in a patient who was first diagnosed with Sjogren's syndrome (SjS). The delay in the diagnosis of CADM caused the ILD to progress into a hypoxemic respiratory failure that made the differential diagnosis more challenging, particularly in the current context of coronavirus infection disease 2019 (COVID-19) pandemic.

Case presentation

Forty-eight-year-old North African man presented at the emergency room with fever, generalised arthromyalgias, and dyspnoea. A first examination revealed an oxygen saturation of 91% on room air leading to an oxygen support requirement. Because of ongoing coronavirus disease (COVID-19) pandemic, the patient was first tested for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in nasopharyngeal sample with real-time RT-PCR (Reverse Transcriptase Polymerase Chain Reaction) with a negative result.

A thorough anamnesis revealed that five months before admission, the patient developed shortness of breath, cough, retrosternal burns, xerophthalmia and xerostomia. The patient was a non-smoker. He consulted a pulmonologist who ordered a pulmonary Computed tomography (CT) scan that suggested an ILD, an eye examination that revealed a low Schirmer test and a labial salivary gland biopsy that showed a focal lymphocytic sialadenitis with a focus score of 1. Immunological tests revealed negative antinuclear antibodies by indirect immunofluorescence (IIF) and positive anti-Ro52 antibodies with medium intensity by immunodot assay. Patient was tentatively diagnosed with primary SjS and treated with prednisone and Azathioprine for one month. Respiratory symptoms improved but did not fully resolve. A month prior to admission, the patient developed a grade 4 dyspnoea on Medical Research Council scale.

Physical examination showed a heliotrope rash, Gottron's papules, a fissured hyperkeratosis ("mechanic hands") of both hands and symmetrical arthritis of the interphalangeal joints (**Figure 1**). The muscular testing showed a mild proximal weakness. Chest X-ray showed bilateral ground glass opacities.

The first laboratory findings showed increased inflammatory markers, normal blood count and renal function.

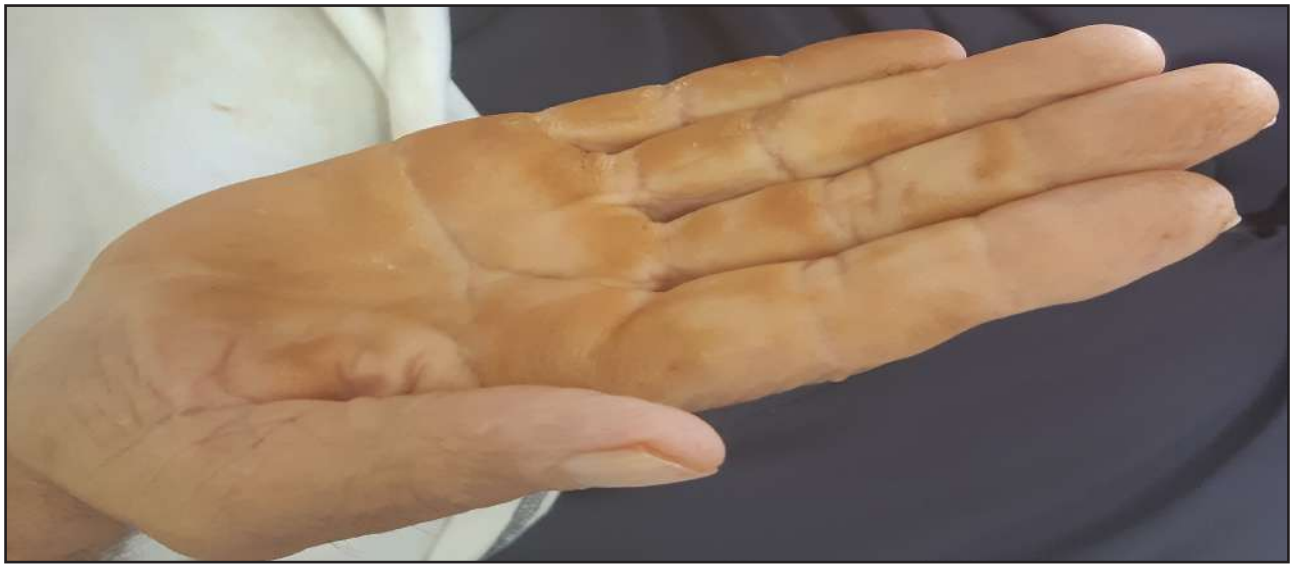

Figure. 1 : Thickened, hyperkeratotic, and fissured aspect of one patient's hands.

Creatine kinase and lactate dehydrogenase were at the upper limit of the normal range. Liver function tests showed cholestasis with a mild hepatic cytolysis (1,5 times normal values). Laboratory findings are summarized in Table 1. Bacterial cultures of bronchoalveolar lavage (BAL) were negative as well as a multiplex RT-PCR for respiratory viruses. Thyroid function tests were normal. Etiological exploration of cholestasis showed negative serological tests of HIV, HBV, HCV and CMV, as well as negative antibodies to autoimmune liver diseases tested by IIF on rodent tissues and immunodot assays. The abdominal ultrasound showed no abnormality as well. An echocardiography and an electrocardiogram were additionally performed to explore the retrosternal burns and showed no abnormalities.

Thoracic CT revealed diffuse interstitial inflammatory changes with the presence of bilateral ground-glass opacities predominantly in the lung bases (**Figure 2**). A restrictive ventilatory defect was evidenced by pulmonary function test with a FVC (forced vital capacity) of 29%. A bronchoscopy did not show any abnormality. Considering the patient lives in a tuberculosis endemic country, Koch bacillus testing in sputum, interferon-gamma release assay (IGRA) and tuberculin skin test were performed and were all negative. Sarcoidosis was considered but serum angiotensin converting enzyme and calcium, as well as the CD4/CD8 ratio in BAL were normal. Given the association of ILD with cutaneous and systemic symptoms, further tests were run to support the etiological investigation. A dermatomyositis was recalled but the results of the explorations were inconclusive. The electromyogram (EMG) indicated subtle myopathic changes and muscle biopsy showed only a slightly dystrophic pattern. Repeated IIF did not detect antinuclear antibodies and the immunoblot was negative for anti-PM-Scl, anti-Ku, anti-Mi2, anti-SRP as well as anti-synthetase antibodies.

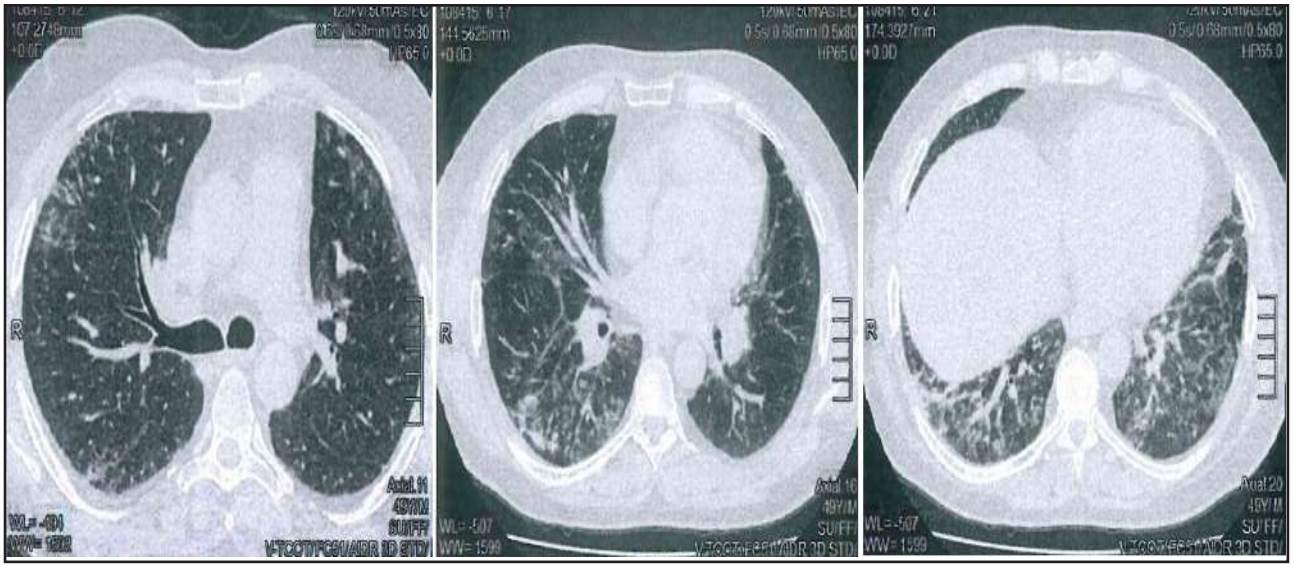

Figure. 2 : Chest CT upon admission shows diffuse ground-glass opacities of the middle lobe and the two lower lobes.

The isolated SjS previously diagnosed could hardly explain the severity of the RP-ILD and the presence of the heliotrope rash. Based on the above clinical evidence, a hypomyopathic DM was suspected. A second immunoblot assay was ordered to test additional myositis specific autoantibodies (MSAs) using Immunoblot *EUROLINE autoimmune inflammatory myopathies 16 Ag (IgG) profile (EUROIMMUN®,* Lübeck, Germany) Anti-MDA5 antibodies revealed positive this time and a CADM was diagnosed. The screening for an underlying cancer was negative.

The patient received 3 days of steroid treatment (500 mg per day of methylprednisolone) followed by prednisolone (60 mg per day). A cyclophosphamide pulse therapy (1 g per day) was also administered to induce remission. After a week of treatment, the patient's laboratory tests, and muscular testing improved and gradually normalized (Table 1). He was still unable to wean off nasal cannula as his oxygen saturation was 93% on room air. He was eventually discharged with a home oxygen therapy.

Eighteen months after discharge, patient was under prednisone (20 mg per day) and Azathioprine as a steroid-sparing agent (150 mg per day). A remarkable improvement in respiratory symptoms, in lung CT and lung function tests was noted during follow-up.

DISCUSSION

We report a case of hypomyopathic DM presenting with positive anti-MDA5 antibodies, RP-ILD, arthritis and mechanic hands in a forty-eight-year-old North African man. Cases of anti-MDA5 antibody-positive DM have been mainly reported in Asians and Caucasians but African origin seem to be also frequent (3).

Anti-MDA5 antibody-positive DM commonly presents with characteristic cutaneous symptoms as ulcerations, palmar papules, heliotrope rash or Gottron's papules (1). Although once considered as a pathognomonic sign of the anti-synthetase syndrome, mechanic hands are frequently described in anti-MDA5 antibodies associated DM (3). Patients frequently exhibit systemic symptoms like fever, generalised arthro-myalgias with minor or no proximal muscle damage and bilateral symmetric arthritis that can recall rheumatoid arthritis (1). Patients also demonstrate ILD with an estimated frequency of 72.7%(1). Depending on the phenotype of the anti-MDA5 antibody-positive DM, it can be a RP-ILD associated with a high mortality rate. Three phenotypes have been described with different prognosis (3). In this case we reported, the patient presented with RP-ILD and mechanic's hands, thus his DM could be classified as a cluster 1, called RP-ILD cluster, according to Allenbach *et al*. (3). Nonetheless, this case could also be classified as a cluster 3, called vasculopathy cluster as this subgroup mainly includes men and is associated with skin manifestations, proximal weakness, relatively few RP-ILD and an intermediate prognosis (3, 4). This classification was also suggested by Nombel et al. and the case could be classified as a phenotype 2 or 3 (4). These classifications aimed to evaluate the prognosis of patients with anti-MDA5 antibodies DM. However, the heterogeneity of clinical presentation complicates the classification of patients according to the proposed phenotypes. The characteristics of each cluster should be clearer to facilitate its use in routine.

Interestingly, besides cutaneous symptoms and ILD, our patient presented with retrosternal burns that were probably related to oesophageal involvement since cardiac tests were normal. Oesophageal involvement seems to be more frequent with age (5). Although rare, cardiac involvement needs to be excluded in patients with CADM as the occurrence of myocarditis may be fatal(6). Remarkably, our patient exhibited elevated liver function tests. These findings have already been reported in patients with anti-MDA5 antibody-positive CADM in the absence of use of hepatotoxic therapy and any abnormalities in liver biopsy (1). As in our patient, liver function tests seem to normalize over time (1).

When he first consulted a pneumologist, our patient did not exhibit characteristic signs of DM. He only presented with an ILD and systemic symptoms, neither one being specific to DM. ILD can be found in numerous heterogenous disorders as sarcoidosis or several connective tissue diseases including SjS (7). The patient had little evidence of myositis which made the diagnosis of DM challenging. Unlike classic DM, anti-MDA5 antibody-positive patients have lower risk of muscle weakness and elevated muscle enzymes (8).

Furthermore, anti-MDA5 antibodies identification can be complex. The characteristic IIF pattern seems to be a finely granular cytoplasmic staining in few, clustered cells (**Figure 3**) (4). While reported as the most typical pattern of anti-MDA5 antibodies, this pattern is incon-

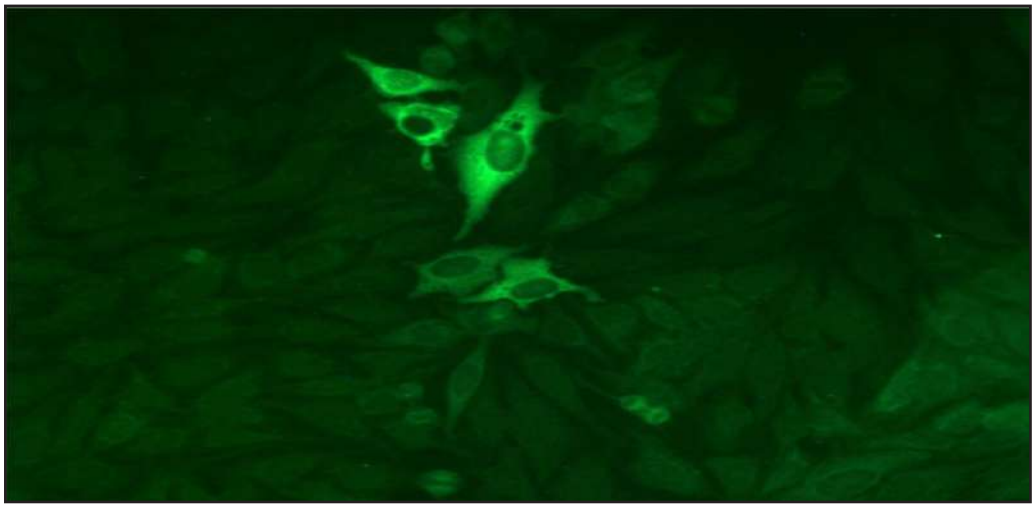

Figure 3 : Indirect immunofluorescence patterns of HEp-2 cells stained with anti-MDA5 positive sera. Typical fine granular cytoplasmic staining in rare clustered cells (4). © 2021 Nombel, Fabien and Coutant, CC-BY 4.0.

stant as it is found in only 50% of cases (4). Other non-specific IIF patterns have also been described as nuclear speckled or cytoplasmic staining of all cells, but could be related to the presence of other antibodies, or to different sources of Hep2 cells differentially expressing MDA5 (4, 9). Besides, as reported in our case, anti-MDA5-positive sera could also be negative by IIF (9). This inconstant IIF pattern of anti-MDA5 antibodies, added to the well-known complexity of reading and interpreting IIF assays, makes the recognition of these antibodies tricky. Consequently, unless DM is suspected, it is hard to find anti-MDA5 antibodies thus the importance of providing clinical information to the biologist to direct them to the most appropriate technique for the diagnosis.

Whatever the IIF aspect, when the clinical context is evocative, a specific assay needs to be performed. Immunoprecipitation (IP) is considered as gold standard for anti-MDA5 antibody testing, but remains time consuming, and expensive (4). For routine diagnostic, immunodot assays are commercialised: line-blot by EUROIMMUN, Lübeck, Germany and dot-blot by D-Tek, Mons, Belgium, as well as an enzyme-linked immunosorbent assay (ELISA) (MESACUP^{TM} anti-MDA5 TEST, Medical & Biological Laboratories, Tokyo, Japan). Immunodot assays have been demonstrated to have high agreement with IP, with reported specificity of 96-99% and sensitivity of 75-93% (4, 10). A particle-based multi-analyte technology (PMAT) (Aptiva®, Inova Diagnostics, CA, USA) is currently available but for research use only.

This case could also evoke an anti-synthetase syndrome in its hypomyopathic form. It presents with fissured hyperkeratosis (mechanic's hand), symmetrical arthritis and severe ILD (11) Therefore, it can be difficult to clinically distinguish it from anti-MDA5 antibody-positive CADM. Anti-synthetase antibodies were, however, negative in our patient.

What helped recall the diagnosis of CADM in our patient was the heliotropic rash, the severe ILD and, curiously, the positive anti-Ro52 antibodies. Although not specific and only suggestive of an underlying autoimmune condition, anti-Ro52 are the most frequent myositis-associated antibodies and are frequently found in CADM patients (12). Anti-Ro52 are also associated with a higher risk of interstitial lung damage regardless of the autoimmune disease concerned (13).But in CADM, they seem associated with RP-ILD and poor prognosis (12, 14).

The diagnosis of anti-MDA5 antibody-positive myositis can be challenging, sometimes mimicking a viral pneumopathy, and the COVID-19 pandemic has only added to its complexity. Clinically, both diseases can present with fever, fatigue, severe ILD possibly leading to hypoxemic respiratory failure, arthralgia, myositis and skin rash (8, 15, 16). Laboratory findings frequently show hyperferritinemia and a significant increase in inflammatory cytokines in both conditions (15, 17). Chest CT show comparable images in such diseases (15, 16). Such clinical similarity is not surprising since both diseases are assimilated to type I interferonopathy (18). Interestingly, MDA5 is as a Retinoic Acid Inducible Gene-1 (RIG-I)-like receptor that is a major intracellular sensor for coronaviruses' RNA, SARS CoV-2, MERS and SARS (19–21). Once activated, MDA5 triggers a signalling cascade through the adaptor mitochondrial antiviral-signalling protein (MAVS) that ultimately leads to type I and type III IFN production (19, 20). Unlike other signalling receptors as RIG I or cGAS, MDA5 has been demonstrated to be essential for anti-SARS CoV-2 immunity (19).

It is now well known that MDA5 pathway is activated in SARS CoV-2 infection. A recent publication further suggested that the MDA5 signalling might be persistently over-activated in severe COVID-19 patients after demonstrating sustainable high titres of anti-MDA5 antibodies in such patients unlike non-severe patients (22). The link between COVID-19 and MDA5 protein is also highlighted on the genetic level, as gene variants in IFIH1 (IFN induced with helicase C domain protein 1), the encoding gene for MDA5 protein, could increase type I interferon production thus activating antiviral defences and potentially increasing resistance to COVID-19 infection at the cost of higher risk for autoimmune diseases (23).

The pathogenesis of DM with anti-MDA5 antibodies is more likely to be multifactorial, involving an unidentified viral trigger, including SARS Cov-2, on a background of genetic susceptibility culminating in an acquired type I interferonopathy.

Besides viral infections, MDA5 has been shown to be activated in autoimmune and autoinflammatory disorders (24). However, the role of anti-MDA5 antibodies in the pathogenesis of DM is still unknown. A pathogenic role may be suggested by in vitro studies of anti-MDA5 antibodies effects on endothelial and pulmonary cells, but is yet to be confirmed by further experiments (25). Additionally, anti-MDA5 antibodies titres were proven to correlate with disease activity and predicts treatment response and disease outcome in anti-MDA5 antibody-positive DM patients (26).

Patients with anti-MDA5 antibody-positive myositis complicated by RP-ILD suffer high early mortality and it is therefore crucial to initiate early aggressive therapy made of a combination of high-dose steroids and immunosuppressants. Cyclophosphamide, mycophenolate mofetil and/or calcineurin inhibitors have been reported to improve survival rate, though 25% of

patients with RP-ILD did not survive (12, 27). For severe RP-ILD, Rituximab has been successfully used (28). The success of B cell depletion can be explained by the pathogenic potential of anti-MDA5 antibodies, as their titre was demonstrated to correlate with disease activity, prognosis and therapeutic response (26). After cyclophosphamide treatment, our patient showed significant improvement of his respiratory condition up to 18 months follow-up period. This favourable evolution constitutes another peculiar aspect of this case as anti-MDA5 antibody associated ILD are usually associated to poor prognosis. In refractory RP-ILD, lung transplant can be the ultimate lifesaving therapy (12, 28).

CONCLUSIONS

This case highlights how challenging it can be to accurately diagnose anti-MDA5 antibody-positive dermatomyositis since early diagnosis and treatment are keys to improve the prognosis of the disease. Its variable and atypical presentation can mislead the diagnosis and cause delays in treatment initiation. The ongoing COVID-19 pandemic makes this diagnosis harder because of the remarkable similarity in its clinical phenotype with anti-MDA5 antibody-positive dermatomyositis.Thus, it is important to keep in mind the possibility of positive anti-MDA5 antibodies in patients presenting hypoxemic respiratory failure in whom the most frequent aetiologies have been ruled out.

Declarations

Ethics approval and consent to participate :
Not applicable

Consent for publication : Written informed consent was obtained from the patient for publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

Availability of data and materials : Not applicable

Competing interests: The authors declare that they have no competing interests.

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Authors' contributions : ZM, DB and TL treated the patient, analyzed and interpreted the patient data. MH performed the laboratory work. IZ and ABH contributed to interpreting immunological tests as well as the gathering of clinical information. FK and IZ prepared the figures, wrote and edited the manuscript. All authors read and approved the final manuscript.

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