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Idiopathic Inflammatory Myopathies: A Case of a Woman with Antisynthetase Syndrome

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Abstract: ***Antisynthetase Syndrome (ASS) is a rare disorder characterized by myositis, Raynaud's phenomenon, fever, interstitial lung disease, mechanic's hands and arthropathy associated with the presence of antibodies against aminoacyl transfer RNA synthetases (anti-ARS), especially anti-Jo-1. Patients with progressive interstitial lung disease have a poorer prognosis and lung involvement is the leading cause of morbidity and mortality. Presence of "Mechanic's hands" with hyperkeratosis on the palmar side of the fingers and fissuring at their tips and radial margins, is an important diagnostic manifestation of this syndrome. Early diagnosis followed by immunosuppressive therapy can significantly improve the health status of these patients and increase their quality of life. This article reviews some of the most important pathophysiologic, clinical and diagnostic features of Inflammatory Idiopathic Miopathies and presents the case of a woman with myalgia, malaise, cough, chest pain and skin involvement who was diagnosed with Antisynthetase Syndrome and received systemic treatment.***

Keywords: MIOPATHIES, ASS

1. Introduction

The idiopathic inflammatory myopathies (IIM) are a heterogeneous group of systemic autoimmune rheumatic disorders characterized by chronic muscle weakness, fatigue, decreased endurance and presence of mononuclear cell infiltrations. They affect primarily the trunk and proximal muscles with a symmetric distribution, often with a subacute or insidious onset; other organs and systems (lungs, joints, heart and esophagus) could be involved[1-2].

Based on different clinical and histopathological features the idiopathic, inflammatory myopathies can be sub-classified into three major groups, polymyositis (PM), dermatomyositis (DM) and inclusion body myositis (IBM)[3]. Annual incidence rates for IIM vary from 2.18 to 8.7 per 10[6;4]. Women are more affected than men, and female to male incidence rate ratio in PM/DM varies between 1.5 and 2.4[5], although in IBM prevalence rates are higher in men compared to women[6] Peter and Bohan criteria are used for diagnosis of PM/DM and Griggs[7] criteria for diagnosis of IBM.

Disease etiopathogenesis is unknown and could be due to a combination of genetic and environmental factors. Among genetic risk factors the presence of HLA-DRB1*0301 and HLA-DQA1*0501 are the strongest known genetic risk factors for all forms of myositis in whites[8-9]. HLA-DRB1*08 allele is the strongest risk factor for African-Americans[9] whereas some alleles are protective like HLA-DRB1*0301 for Japanese population[10].

Polymorphisms in the tumor necrosis factor α (TNF-a) (TNFa-308A) allele have been associated with a longer disease course, increased disease severity, and calcinosis in Juvenile dermatomyositis (JDM)[11,12] and there are reports of association of IL-1 polymorphism in children with juvenile dermatomiositis[14]. UV light could be a risk factor for development of DM. Studies have shown a positive correlation between UV light exposure and DM patients with anti–Mi-2 autoantibodies. Viral infections, such as with Coxsackie B virus, may trigger the onset of immune disregulation in the genetically susceptible host[13] but no clear association has been established between infectious agents and chronic inflammation.

Inflammatory myopathies can occur in association with other autoimmune connective tissue diseases such as scleroderma, systemic lupus erythematosus (SLE), rheumatoid arthritis, Sjögren's syndrome, polyarteritis nodosa, and sarcoidosis. Significant proportions of all myositis patients (11% to 40%) have an associated connective tissue disease[15-17].

Disease pathogenesis is complex and studies show that it might involve both immunological (humoral and inflammatory cell immediated) and non immunological (Endoplasmic reticulum stress and hypoxia) mechanisms.

In PM and IBM inflammatory cellular infiltrates consisting primarily of CD8+ T cells, macrophages and dendritic cells and are mainly located in the endomysium surrounding muscle fibers. In DM infiltrates are composed of CD4+ T cells, DCs, and macrophages, with occasional B cells and are situated in the perimysial areas.

The varying inflammatory cell infiltrate compositions and the fact that they are located in distinct sites suggest the existence of two different pathogenic mechanisms that cause myositis : one mediated through T lymphocytes (CTLs) - directed against muscle fibers, predominating in PM and IBM, and the other directed against vessels, predominating in DM.

In the early fazes of DM the complement cascade is activated. Lytic membrane attack complexes are deposited in the endothelial cells and the eventual loss of capillaries occurs. Capillaries show clear hyperplasia, vacuolization, and necrosis, contributing to an ischemia that could cause

fiber damage [19,20], they are abnormally thickened and enlarged and look like high endothelial venules, which are characteristics of vessels that facilitate lymphocyte trafficking. They also show signs of neovascularization[21]. A microscopic feature highly characteristic of DM is perifascicular atrophy secondary to microvascular damage[18].

In PM and IBM immunoelectron microscopy showed that CD8+T cells and macrophages transverse the basal lamina, focally compress the fiber and ultimately replace entire segments of the muscle fiber. All of the invaded and some non invaded fibers express increased amounts of HLA class 1[22].

MHC class I staining is usually observed on the sarcolemma and sometimes sarcoplasm of muscle fibers of patients with myopathy [24.25]. Because MHC class I assembly occurs in the ER and because up regulation in myositis muscle fibers is widespread, even in the absence of visible inflammatory infiltrate, it is likely that ER stress plays a role in the muscle fiber damage and dysfunction associated with human myositis. Over expression of MHC class I on muscle fibers results in activation of the NFκB and ER stress response pathway in human inflammatory myopathies and in the mouse model of myositis [26,27].

Muscle hypoxia, which may result from capillary loss and local tissue inflammation may contribute to the clinical symptoms and muscle fatigue and might be associated with disease mechanisms in inflammatory myopathies[25].

Various proinflammatory cytokines like: IL-1alpha, IL-1beta and TNF-alpha and HMGB1 have been detected in muscle tissues of myositis patients. IL-1α was suggested to play a role in myofibrillar protein break-down and muscle regeneration; however, these claims are yet to be proven[28]. The pathogenic role of TNF-α in myositis muscle was not completely understood; however, it has been hypothesized to attract immune cells by enhancing transendothelial cell trafficking in affected muscle[29]. In addition, TNF-α has been hypothesized to activate immune cells and induce MHC class I expression in the myositis muscle. The DNA-binding high mobility group box 1 (HMGB1) protein was found to exhibit both extranuclear and extracellular patterns in the muscle tissue of patients with PM and DM. Exposure to HMGB1 induced a reversible upregulation of MHC class I in the muscle fibers and irreversible decrease in Ca2+ release from the sarcoplasmic reticulum during fatigue, implicating a role of HMGB1 and MHC class I early in the pathogenesis of IIMs[30]. The importance of different cytokines and chemokines in the disease mechanisms of myositis is still to be clarified but they constitute potential targets for development of new therapies.

Autoantibodies are present in more than 50 % of patient with IIM and are referred to as myositis-specific autoantibodies (MSAs) and myositis-associated autoantibodies (MAAs). The MAAs is not specific for IIM, and are found in a variety of autoimmune diseases. Some MAAs are anti-snRNP, anti-Ro/SSA, anti-Ku, and anti-PM/Scl.

MSAs are specific for inflammatory myopathies, their presence has been associated with distinct clinical phenotypes. These clinical phenotypes offer another approach to define homogeneous patient groups and to subclassify myositis, both of which could be helpful for diagnosis and for understanding disease mechanisms [34-36].

Some of the MSAs, their target structures and the clinical subgroups they are associated with are : **1). Anti-aminoacyl-tRNA synthetase antibodies**, also known as antisynthetase antibodies or anti-ARS, directed against a cytoplasmic group of 20 enzymes, essential for protein synthesis and cell viability[32].The anti-ARS autoantibodies define the anti-synthetase syndrome (ASS) **2)**. Antibodies associated with adult dermatomyositis, which include **anti-Mi-2 antibodies** directed against components of a nucleosome remodeling complex[31], **Anti-155/140** targeting TIF1-γ and **Anti-NXP-2 3)**. Antibodies associated with acute necrotizing myopathy comprising anti signal recognition particle or **anti-SRP antibodies** directed against ribonucleoproteins involved in translational transport and **Anti-200/100** antibodies **4)**. Antibodies associated with amyopathic dermatomyositis, including : **Anti-SAE** and **Anti-MDA5 antibodie**s directed against a cytoplasmic RNA helicase that belongs to the retinoic acid-inducible gene-I (RIG-I) family [37-38].

Antisynthetase syndrome is a subgroup of IIM characterized by the presence of antisynthetase autoantibodies, myositis, interstitial lung disease, Raynaud's phenomenon, nonerosive symmetric polyarthritis of the small joints, fever and mechanic's hands.

Anti-ARS antibodies are directed against cytoplasmic enzymes that catalyze the formation of the aminoacyl-tRNA complex from an amino acid and its cognate tRNA. To date, eight different anti-ARS antibodies have been described: anti-PL-7 (anti-threonyl-tRNA syntethase)[39]; anti-PL-12 (anti-alanyl-tRNA syntethase) [40]; anti-OJ (anti-isoleucyl-tRNA syntethase)[41]; anti-EJ (anti-glycyl-tRNA syntethase)[41]; anti-KS (anti-asparaginyl-tRNA syntethase)[42]; anti-ZO (anti-phenylalanyl-tRNA syntethase)[43]; anti Ha (anti-tyrosyl-tRNA syntethase)[44]; and anti-Jo-1 (anti-histidyl-tRNA syntethase).[45] All of these antibodies are directed at functionally related enzymes and are mutually exclusive in a given patient. Anti-Jo-1 is the most common anti–ARS antibody, it is found in 20–30% of PM patients, in 5–10% of those with DM[46] and in 75% of all reported cases in which an anti-ARS is present.

This article reports the case of a woman with proximal muscle pain, chest pain, cough and skin involvement. She was diagnosed with ASS and received therapy with glucocorticosteroids and an immunosuppressive agent.

2. Case

A 50 years old woman presented at the clinic, complaining of severe proximal muscle weakness, fatigue and malaise. Patient explained that her problems started 6 months ago, after a hiking trip that she made with her son, when she felt burning pain in both her legs and thigh muscles. She assumed the disorder was due to increased physical exertion and that it would subside spontaneously in a couple of weeks, so she did not seek further medical assistance. Weeks

went by but her situation did not improve. She felt progressively worse, and within a couple of months the initial leg pain was transformed into a full-blown inability to walk uphill, climb stairs and rise from chairs. Daily activities became a burden, pain and muscle weakness were constantly present and other problems started to immerge. Her hands became hard, scaly and fissuring, fingers felt sore and stiff and a decrease in their agility and suppleness made them look more mechanic than real; they changed color from time to time and exposure to cold temperatures felt very uncomfortable. Subsequently she developed persistent cough, breathlessness and chest pain. Her energy level was low and her poor health status decreased substantially her quality of life and performance, so she decided to go and see her general practitioner, who after examination recommended an immediate consultation with a rheumatologist…

During anamnesis vitae, patient explained that she was widowed, lived alone, had a healthy son and no siblings. Her family history was unremarkable; she had had no contact with known toxins lately, had smoked for 20 years but abstained in the last 2 years, had never used illicit drugs or received new medications. She suffered also from psoriasis and had no drug allergies.

Physical examination showed that she was a 172 cm tall woman, weighted 70 kg and had pale skin; her head and neck were free without enlarged lymph nodes and the patient looked weakened and fatigued. Patient had macular erithemas on her arms and legs and Raynauld's phenomenon. Her eyes, ears, nose, and throat, examination was unremarkable. Below are listed the results of her systems examination and laboratory and immunological tests.

Vital Signs and General Examination: Blood pressure 144/80 mmHg, heart rate 72 beat/min; respiratory rate 18 breaths/minute; T 38.4° C, Normostenic individual.

Mental status: Reduced concentration span. Frequent mood swings and sleep disorders.

Cardiovascular System: Regular heart rate and rhythm; normal S1 and S2 sounds with no murmurs or audible rubs.

Abdomen: Abdomen was soft, not tender, and not distended, Blumberg (-)

Gastrointestinal System: Normal bowel sounds, liver is palpated 2 cm under right costovertebral angle, no spleen enlargement. Patient relates that she has no dispepsia, pyrosis, or digestive disorders, and no weight loss

Genital & Urinar System : No pain or burning during urination. Pasternacki (-) on both sides.

Respiratory System : Frequent coughing, dispnea, chest pain, fever and reduced physical exercise tolerance.

Musculosceletal examination: Weakness and pain in the muscles of her lower extremities, neck and trunk. Patient finds rising from a chair and walking upstairs difficult. PIP and MCP joints tender and painful in palpation. Spondyloarthrotic changes L3-S1.

Skin: Livedo reticularis, hiperceratosis and fissuring in her fingers, mechanic hands, macular erythemas in the arms and legs. Hair loss.

Lab test results: Slightly elevated Creatine Kinase (7 fold elevation); increased Lactate Dehidrogenase (3 fold elevation) and increased Aldolase levels; ALT and AST mildly elevated; ESR 50 mm/h; CRP 2 mg/dl.

Immunological test results: Anti nuclear Antibodies (ANA) : (+) 1:160; Anti ds DNA antibodies : (-); IgG anticardiolipin antibodies (-); IgM anticardiolipin antibodies (-); Anti Jo-1 antibodies: (+); Rheumatoid Factor: (-)

High-resolution computed tomography (HRCT) and pulmonary function tests showed pulmonary involvement characteristic of Intestinal Lung Disease, basal crackles and restrictive pattern in pulmonary functional tests (reduced VC, FVC and DLco)

Muscle biopsy and EMG, were also performed and they showed changes characteristic of inflammatory myopathies**.** Based on the clinical features of the patient including the presence of myositis, interstitial lung disease (ILD), Raynaud's phenomenon, non-erosive symmetric polyarthritis in small joints, and scaly skin changes on hands the diagnosis of Antisynthetase Syndrome was established and treatment was started immediately.

Patient was treated with glucorticosteroids, calcium and vit D supplements and cyclophosfamide. Complete blood cell count, liver enzyme function tests, and creatinine measurements were obtained regularly. Patient reacted well to this choice of therapy; her muscle function, VC, FVC, general wellbeing and CK levels improved. Medication dosages were reduced in accordance with her improved health. Patient was advised to exercise regularly. She is kept under observation and her health status is currently stable.

3. Discussion

Antisynthetase Syndrome (ASS), is the largest subgroup in the category of Idiopathic Inflammatory myopathies. It was described firstly by Marguerie et al. in 1990 and is currently characterized by the presence of antibodies to tRNA synthetase with anti-Jo-1 being the most common, myositis, interstitial lung disease, joint disease, fever, Raynaud's phenomenon and "mechanic's hands" [48,49].It is a rare disease, incidence in general population is still unknown[47], the age at onset among adults ranges from 19 to 82 years with a mean age at onset varying from 43 to 60 yrs[70,71,72,73,74]. Very few children and adolescents with ASS have been reported. A female dominance, with about twice as many females as men affected, has been found in most series[71,72,73].

The adverse clinical outcome, with relatively high morbidity and mortality rates compared with those of other forms of inflammatory myosites, is primarily due to irreversible

damage of the lung parenchyma, manifested as interstitial lung disease[50, 51, 52–54].

Interstitial lung disease (ILD) refers to a broad category, comprising more than 100 lung disorders which are categorized based on their know or unknown causes and further grouped based on specific exposures, association with systemic disease, or relation with a known genetic disorder. Idiopathic ILD includes two entities: cases that do not represent idiopathic interstitial pneumonia (IIP), owing to recognition of associated conditions or underlying exposures, and cases that could represent IIP [55].

Some of the most common clinical entities and the corresponding HRCT patterns and histological features observed in patients with ASS are: **1)** Cryptogenic Organizing Pneumonia **(COP),** characterized by patchy consolidations and/or nodules[56-61]; the majority of histopatological changes center on small airways. There is a mild associated interstitial inflammatory infiltrate, type II cell metaplasia, and an increase in alveolar macrophages, some of which may be foamy. A small amount of airspace fibrin may be focally present. There is relative preservation of background lung architecture [62-65] **2)** Usual Interstitial Pneumonia **(UIP),** characterized by honeycombing and traction bronchiectases [56-61]; key histologic features of the UIP pattern are architectural destruction, fibrosis often with honeycombing, scattered fibroblastic foci, patchy distribution and involvement of the periphery of the acinus or lobule[66,67] **3)** Nonspecific Interstitial Pneumonia **(NSIP),** characterized by ground-glass opacities and irregular linear opacities[56-61]; histologic features consists primarily of mild to moderate interstitial chronic inflammation, usually with lymphocytes and a few plasma cells[66,68,69] with/or fibrosis **4)** Diffuse Alveolar Damage **(DAD),** defined by bilateral and extensive consolidation with airspace and ground-glass opacities[56-61] some major histologic features include: alveolar septal thickening due to organizing fibrosis usually diffuse, airspace patchy or diffuse organization; the exudative phase shows edema, hyaline membranes, and interstitial acute inflammation[75,76,77]. Lung involvement might be classified into three groups: type I acute, type II gradual and type III asymptomatic. Immunosuppressive therapy responsiveness varies with different histopathological patterns, UIP, or acute interstitial pneumonia responds poorly to glucocorticoids and other immunosuppressive therapies and have a poor prognosis.

Glucocorticoids (with supplement vitamin D and calcium) remain the first line of therapy for patients with miopathy, dosages vary from 0.75 to 1 (up to 2) mg/kg body weight per day and they should be used for 4 to 12 weeks. Most experts recommend that glucocorticoid treatment be combined with another immunosuppressive drug to reduce the side effects of the glucocorticoids and to boost the immunosuppressive effect. The most frequently used immunosuppressive agents are azathioprine and methotrexate[78].

Other treatments include cyclosporine and mycophenolate mofetil as supported by reviews and studies[79].

Patients who do not respond to standard therapy and have severe disease are treated with intravenous methylprednisolone (IVMP) at dosages of 500 mg to 1000 mg daily for 1-3 consecutive days followed by high-dose oral corticosteroids with taper regimen.

Cyclophosfamide either orally or intravenously is used for cases with severe organ damage and ILD kelley. CYC could be given at: 0.6-1.0 g/m2 IV every 4 wk or 1-2 mg/kg/day orally, for 3-12 months[80]. Rituximab is becoming the alternative for patients who have refractory IIM or severe disease complications. Tacrolimus is another treatment option. Very severe cases could benefit from plasmapheresis. In irreversible, end stage pulmonary disease, lung transplantation appears to be the only therapeutic option.

Hydroxychloroquine is an antimalarial drug administered at 200 mg twice daily (5 mg/kg). It is primarily used for cutaneous manifestations of DM or JDM. For noonresponders, chloroquine can be used at dosages of 250 to 500 mg/d[80].

4. Conclusion

Idiopathic inflammatory miopathies are rare disorders. Their diagnosis requires a very high level of awareness to their specific clinical signs and thorough collaboration between pulmonologists, radiologists and rheumatologists. The presence of ASS should be considered in patients with ILD and undifferentiated connective tissue disease. Patients should be screened for ARS antibodies; particularly in the presence of typical clinical features like “mechanic’s hands”, Raynauld phenomenon and skin manifestations.

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