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Idiopathic inflammatory myopathies and the antisynthetase syndrome

Idiopathic inflammatory myopathies (IIM) are a heterogeneous group of diseases whose characteristic features are symmetric muscle weakness, elevated levels of muscle enzymes, inflammatory infiltration found in the muscle biopsy, primary muscle damage as found in electrophysiological examination (8). In 1974 Bohan and Peter classified various inflammatory myopathies.

In 1993 Euwer and Sontheimer suggested inclusion of amyopathic dermatomyositis (ADM) into IIM-spectrum. The diagnosis of ADM should be based on: 1) finding all characteristic and pathognomic clinical cutaneous features of DM, 2) skin biopsy, 3) lack of clinical features of proximal muscle weakness in the shoulders and hips over two years after the onset of the cutaneous symptoms, 4) normal levels of creatine kinase and aldolase for two years after the onset of the disease. Patients with theses symptoms do not meet Peter and Bohan's criteria which are the most commonly accepted attempt at classification of IIM (4,5).

Approximately 8% of patients with DM/PM develop neoplasm, and this particularly affects people over 60. Malignancy in the course of PM in children is uncommon. Malignacies associated with PM/DM typically include: lung cancer, ovaries cancer, breast cancer, gastrointestinal tract cancer and lymphoproliferative syndromes (11). Inclusion body myositis (IBM) is currently also included into IIM-spectrum (8).

ETIOPATHOGENESIS

Etiopathogenesis of inflammatory myopathies is still unclear, although immune abnormalities are known to be at their core. Both genetic and environmental factors are likely to play a role by inducing the cell and humoral immune response which manifests clinically as muscle damage.

There are numerous factors which have been suggested to be associated with the development of IIM. The acute onset, resembling a viral infection, may indeed be associated with an infection. Picornaviruses (Coxackie viruses and echoviruses) may probably take part in inducing the autoimmune process. Although viral elements were not found in muscle biopsies, there is indirect serological, ultrastructural and animal model evidence suggesting the role of viruses in the pathogenesis of idiopathic inflammatory myopathies. The theory of the viral infection assumes three hypotheses: 1) production of antibodies through immune molecular mimicry, 2) similarity or complementarity between the virus's proteins or RNA and the host's proteins or RNA, 3) participation of antiidiotypic antibodies. In antisynthetase syndrome there is molecular similarity between histidyl-tRNA synthetase and RNA of picornaviruses (3). During replication in the host's cell, picornaviruses use synthetases. In myocytes, the complexes are created composed of the viral RNA and histidyl-tRNA synthetase, which may lead to production of antibodies. Antisynthetase antibodies may also be directed against viral epitopes "similar" to tRNA.

It has been observed that new incidences of IIM tend to occur in groups, for example in India and Northern America. In the United States, new incidences are observed to show certain seasonality: patients with Jo-1 antibody tend to fall ill in spring, and in those with anti-SRP antibody the onset of the disease is frequently associated with autumn.

Cases resembling PM have been reported among patients with borreliosis, toxoplasmosis, and in the course of adenovirus infections. Environmental factors can also play a role in inducing IIM. They include D-pencillamine which is able to provoke a clinical syndrome with the same pathological picture and serological reactions as in PM, foods such as rape-oil, L-tryptophan, toxins contained in certain fishes, exposure to silicon, and collagen silicon implants. In aetiology of IIM, a certain role is attributed to genetic factors, especially in particular races and ethnic groups. Myositis occurs in Afro-Americans three times as often as in Caucasians. Familial occurrence of IIM is quite rare. The most recent research has shown the presence of HLA locus DRQ closely related to JDM, particularly allele DQA10501of HLA, in patients with JDM from various ethnic groups. Studies carried out in patients from 4 ethnic groups showed an association between MHC class II with incidence of IIM. Their results provide evidence that HLA DRB 10301(DR3), DQA10501 and DQB10201 (DQ2) allele (haplotype) occurred more frequently in Caucasian patients with IIM, mainly with PM, particularly in the cases with co-occurring Jo-1 and other specific antibodies. It seems, therefore, that the predisposition for occurrence of specific antibodies in patients with IIM is associated with HLA DQA1 locus in MHC class II region.

Despite clinical similarities between individual diseases from IIM-spectrum, the involved mechanisms responsible for damage of muscle cells show significant differences. Variability within inflammatory infiltrates is observed with respect to both the number, type and distribution of lymphocytes, which suggests diverse immunopathological mechanisms for individual syndromes. In DM, the humoral response is activated which is manifested in increased ratios of active lymphocytes T helper lymphocytes (CD4+) around the blood vessels. A decrease in the number of capillary vessels is also observed as well as the presence of deposits of the components of C5b-C9 complement. Destruction of the capillary vessels leads to necrosis of muscle cells, which in turn initiates the inflammatory process.

In polymyositis the immune response of the cellular type is prevalent. Inflammatory infiltrates occur in the endomysium and are composed of cytotoxic lymphocytes (CD8+) and macrophages. In healthy muscle cells the expression of HLA antigens of either class I or II is not observed. Increased numbers of HLA class I are presented on the surface of all the muscle fibres to which CD8+ lymphocytes penetrated and on a portion of the unaltered fibres. These fibres are surrounded by cytotoxic lymphocytes and macrophages. Following recognition of their specific antigen, CD8+ lymphocytes are activated and infiltrate muscle cells, leading to release of perforin, granzymyme A and cytokins. Some authors deny existence of apoptosis in muscle cells, accepting only the possibility of necrosis (8).

SPECIFIC AND NON-SPECIFIC ANTIBODIES

Antibodies against nuclear and cytoplasmatic antigens are found in 60–80% of patients with PM/DM (7). Both myositis specific antibodies (MSA) and non-specific, myositis associated antibodies (MAA) are present in IIM. Antisynthetases are one of the most commonly occurring MSA. They are directed against enzymes catalysing the reaction of binding the aminoacid to an appropriate tRNA. Out of 20 synthetases, 7 have been described. One of the most common is the antibody directed against histidyl-tRNA synthetase (Jo-1). It is found in approximately 20% of patients with IIM. In about 1–3% of patients antibodies are found against treonyl-tRNA synthetase (PL-7), alanyl-tRNA synthetase (PL-12), glycyl-tRNA synthetase (EJ), isoleucyn-tRNA synthetase (OJ), anti-asparginyl-tRNA synthetase (KS), and anti-Wa directed against 48 kDa protein which has not been described so far but is associated with amino acyl tRNA (6,7,8). Antisynthetases are immune markers of the so-called antisynthetase syndrome. In some patients KJ antibody is found against an unknown cytoplasmatic protein with a molecular mass of 120 kDa which takes part in synthesis of proteins and translation processes. It occurs in approximately 1% of patients with myositis. Anti-SRP antibody occurs in about 4% of cases. This antigen takes part in the transport of newly synthesized proteins to the endoplasmatic reticulum. Anti-SPR occurs in the patients with PM with a very severe course, commonly with cardiac muscle involvement. Anti-FER (very rare) directed against elongation factor 1alpha-1, and anti-Mas are the antibodies which, so far, have not been

associated with a particular clinical picture. Anti-Mi-2 antibody is the only nuclear antibody in the MSA group and occurs exclusively in DM. Anti Mi-2 occurs in approximately 8–10% of IIM cases and in approximately 15–20% of DM cases in Northern American population. The most reactive component of the antigen, which is a complex of 8 proteins, is a 240 kDa protein. Anti-Mi-2 is less frequently found in children with JDM, and exceptionally – in DM associated with malignancy. DM associated with anti Mi-2 is benign and responsive to corticosteroid therapy.

Non-specific antibodies in inflammatory myopathies (MAA) include anti-56kD, Pm-scl, anti-ku, U1RNP and anti-Ro. U1RNP is characteristic of MCTD (i.e. overlap syndrome) in which features of SLE, scleroderma, polymyositis and rheumatoid arthritis co-occur. In 20% of patients anti-Ro antibody is found, either as the only one or as co-occurring with MSA. PM-Scl occurs mainly in scleroderma-PM overlap syndrome. It is directed against a complex of 11 proteins localised in the nucleoli and nucleus. The clinical features of both disorders in 50–70% of cases co-occur with PM-Scl antibody. It is interesting that other antibodies characteristic of scleroderma and PM do not occur with PM-Scl. Błaszczyk et al. consider PM-Scl a marker characteristic of scleromyositis (SclM), an overlap syndrome which should be diagnosed as a separate disease (8).

The diagnosis of IIM is possible when 4 out of the above 5 criteria are met. In 1997 Targoff and al. suggested that the presence of serum MSA antibodies be included into the diagnostic criteria. Adding MSA to these criteria enables confident diagnosis of PM without the biopsy and DM without the necessity of performing EMG or the biopsy (1, 7).

SYSTEMIC CHANGES IN IIM

Inflammatory myopathies are typically characterized by an acute onset, fever reaching 39°C, fatigue, depression, joint pain, arthritis leading to deformations, and Raynoud's symptom. The most common changes in the circulatory system include: cardiomyositis, conduction blocks, heart rhythm abnormalities. Right-and left venticular circulation insufficiency may lead to cardiomyopathy, *cor pulmonale* and hypoxemia. In the respiratory system, restrictive changes are relatively common, secondary to muscle weakness.

Aspiration pneumonia is a result of weakness of larynx and upper oesophagus muscle. The incidence of interstitial lung disease (ILD) ranges from 5 to 47% depending on the investigated patient samples and duration of the disease. Histological examination allows differentiation of the following types of ILD: *bronchiolitis obliterans* organizing pneumonia (BOOP), usual interstitial pneumonia (UIP), non-specific interstitial pneumonia (NSIP), common fibrosing interstitial pneumonia (CFIP), and diffuse alveolar damage. Symptoms of ILD comprise a fever, a dry cough, dyspnea, interstitial infiltrate present at the base of the lung apparent in radiography (6, 8). The most common symptoms from the gastrointestinal system include peristalsis abnormalities, gastroesophageal reflux, dysphagia, gastric contents retention, gastric and duodenal ulceration (it may be caused by both chronic corticosteroid therapy and severe vasculitis), and rhino-pharyngeal cavity muscle weakness.

In the endocrine system, it is mainly the thyroid that is involved. Autoimmune thyroiditis and non-toxic goitre have been reported (8). Extensive destruction of the muscle tissue leads to myoglobinuria and acute renal insufficiency (11); calcinosis occurs mainly in children (3).

THE ANTISYNTHETASE SYNDROME

The antisynthetase syndrome is a disorder recognized relatively recently, closely associated with the antibodies directed against synthetases taking part in the translation process by tRNA. It is characterized by the occurrence of interstitial lung disease (ILD), myositis, a fever (in many cases), polyarthritis, Raynaud's phenomenon, and characteristic skin alterations such as mechanic's hands or scleroderma-like changes. Out of 20 synthetases, only 7 have been described, and only anti Jo-1 has been described in detail and can be detected by the basic ELISA method or by immunoprecipitation. The antisynthetase syndrome affects women twice as often as men. An increase in the morbidity during spring has been reported in the U.S. There are similarities in the

incidence of the antisynthetase syndrome between the U.S., Japan and Europe. The theory of a viral infection seems to play a considerable role in the pathogenesis of the antisynthetase syndrome; the group of picornaviruses has most often been suggested as responsible for the infection (6).

In histopathological tests of the muscle from patients with the antisynthetase syndrome, alterations in the perimysium were found, in the form of fragmentation and inflammatory infiltrate composed mainly of macrophages. The endomysium and perivascular areas were unaltered. This pattern of alterations is significantly different from the pattern occurring in idiopathic inflammatory myopathies in which inflammatory changes are localized in the endomysium and perivascular, and the perimysium fragmentation is rare. There is a similarity between the inflammatory infiltrate in the antisynthetase syndrome and in fascitis. The muscular symptoms occurring in the antisynthetase syndrome are frequently preceded by pulmonary or joint symptoms. In 70% of patients with the antisynthetase syndrome, interstitial lung disease occurs. In 80% of patients generalized symptoms are present such as a fever, fatigue, and a body mass loss. Laboratory tests are often indicative of an inflammatory process.

Interstitial lung disease significantly worsens the prognosis in the antisynthetase syndrome. Without treatment, pulmonary fibrosis progresses rapidly. ILD increases mortality by 40%. The first symptoms of ILD are a dry cough and dyspnea on exertion. The most accurate and highly recommended technique for diagnosing ILD is high resolution computed tomography (HRCT). The computed picture in interstitial lung disease usually shows bilateral diffuse alterations, localised at the bases of the lungs. Roughness on the pleura, thickening, hazy density of the ground glass type, concentration areas and linear shadows often indicate lymphocytic bronchiolitis. At this stage of the disease, the symptoms respond positively to corticostroid therapy. Pulmonary fibrosis is manifested by intrabranchial-vascular thickening, Kerley's B lines, concentrations, bronchiectasias and bronchiolectasias, which in HRCT is visible as honey-combing. The honey-combing pattern is indicative of irreversible fibrosis which is often unresponsive to treatment. Lung function testing is very important for early detection of the disease. The earliest symptom is a decrease in DLCO (lung diffusion capacity). DLCO is defined as the ratio of the level of CO_2 diffusion to the alveolus volume. The KCO values lower than 70–75% are indicative of a pathology. The alveolar-capillary gradient is high at rest, and increases on exertion, which causes a decrease in DLCO, also indicative of a pathology. All these abnormalities are characteristic for the destruction of the alveolus-capillary barrier. Bronchoalveolar lavage (BAL) can also provide important information. A high number of CD8+ T cells present in BAL indicates lymphocytic alveolitis (6).

Joint symptoms in the antisynthetase syndrome can range in form from mild pain syndromes to deforming arthritis. The changes usually affect knees, elbows, wrists and hands. In some cases, the rheumatoid factor may be present. Intra-articular calcinations and hydroxyapatite deposits have also been reported.

Raynaud's phenomenon occurs in 2/3 of patients and can precede myositis by several years. Capillaroscopy has shown the presence of neoangiogenesis and giant capillaries, which is a relatively frequent finding in inflammatory myopathies. The prognosis seems to be independent of the presence of antisynthetase antibodies themselves. The presence of interstitial lung disease exerts considerable impact on increase in mortality. In their study of 745 patients with DM and PM, Arsur and Greenberg found that an increase in mortality was associated with the presence of interstitial lung disease. Mortality was 40% for the whole group, 62% for patients with interstitial lung disease (diagnosed on the basis of the biopsy), and 24% for patients without a lung disease (1). The standard treatment of IIM involves prednisolon in a dose of approximately 1 mg/kg/day. If there is no improvement, methotrexat (MTX) should be added. If the disease is still active (as diagnosed by laboratory tests), azatioprin is used. The last resort is intravenous administration of immunoglobulins (9).

Treatment of the antisynthetase syndrome is similar to treatment of inflammatory myopathies and idiopathic pulmonary fibrosis. All joint and muscle symptoms and some types of pulmonary symptoms (BOOP and NSIP) are responsive to glicocorticosteroid treatments. UIP and destruction of alveoli are usually steroid-resistant and require immunosuppressive treatment. In some cases

cyclophosphamid, cyclosporin A and tacrolimus were used with positive effects. Intravenous immunoglubulins, which are secondary treatment in inflammatory myopathies, have not been sufficiently studied in treatment of the antisynthetase syndrome.

Table 1. Bohan and Peter's (2) classification of IIM

Group I	Primary idiopathic polymyositis (PM)
Group II	Primary idiopathic dermatomyositis (DM)
Group III	Dermatomyositis or polymyositis with an associated malignancy
Group IV	Juvenile dermatomyositis (JDM) or juvenile polymyositis (JPM) with co-occurring vasculitis
Group V	Dermatomyositis or polymyositis associated with another connective tissue disease (overlap myositis)

Table 2. Diagnostic criteria for IIM

I	Symmetric weakness of proximal muscles within the shoulder and pelvic girdle
II	Elevated levels of muscle enzymes, i.e. Ck, aldolase, ast, alt, ldh
III	Myopathic EMG – with decreased mean time of potentials of single units, lowered amplitude, decreased surface and increased number of polyphasic potentials
IV	Muscle biopsy with the presence of inflammatory infiltrate in the endomysium and perimysium, degeneration and regeneration, perifascicular loss
V	Typical cutaneous symptoms: Gottron's symptom above all joints, "heliotrope" eyelids, V-sign, rash around the neck, Raynaud's phenomenon, mechanic's hands, changes on nailfolds (tenderness, oedema – Keining's sign), scleroderma-like changes, oversensitivity to UV (7,8)

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SUMMARY

Idiopathic inflammatory myopathies (IIM) are a heterogeneous group of disorders whose characteristic features are symmetric muscle weakness, elevated levels of muscle enzymes, inflammatory infiltration found in the muscle biopsy, primary muscle damage as found in electrophysiological examination. Etiopathogenesis of inflammatory myopathies is still unclear, although immune abnormalities are known to be at their core. Both genetic and environmental factors are likely to play a role by inducing the cell and humoral immune response which manifests clinically as muscle damage. Antibodies against nuclear and cytoplasmatic antigens are found in 60–80% of patients with PM/DM. Both myositis specific antibodies (MSA) and non-specific, myositis associated antibodies (MAA) are present in IIM. Antisynthetases are one of the most commonly occurring MSA. They are directed against enzymes catalysing the reaction of binding the aminoacid to an appropriate tRNA. Antisynthetases are immune markers of the so-called antisynthetase syndrome. The antisynthetase syndrome is a disorder recognized relatively recently; it is characterized by the occurrence of interstitial lung disease (ILD), myositis, a fever (in many cases), polyarthritis, Raynaud's phenomenon, and characteristic skin alterations such as mechanic's hands or scleroderma-like changes.

Idiopatyczne miopatie zapalne ze szczególnym uwzględnieniem zespołu antysyntetazowego

Idiopatyczne miopatie zapalne (*idiopathic inflammatory myopaties* – IIM) są heterogenną grupą chorób, których cechami charakterystycznymi są: symetryczne osłabienie mięśni, podwyższony poziom enzymów mięśniowych, nacieki zapalne stwierdzone w biopsji mięśniowej, uszkodzenie pierwotne mięśni stwierdzone w badaniu elektrofizjologicznym. Etiopatogeneza miopatii zapalnych wciąż jest nieznana, wiadomo jednak, że ich istotą są zaburzenia immunologiczne. Prawdopodobnie odgrywają tu rolę czynniki genetyczne i środowiskowe, które indukują odpowiedź immunologiczną zarówno komórkową, jak i humoralną, klinicznie objawiającą się uszkodzeniem mięśni. U 60–80% chorych z PM/DM wykrywane są przeciwciała skierowane przeciwko antygenom jądrowym i cytoplazmatycznym. W IIM obecne są tzw. przeciwciała swoiste dla miopatii zapalnych (*myositis specific antibodies* – MSA) oraz przeciwciała nieswoiste, związane z miopatiami zapalnymi (*myositis associated antibodies* – MAA). Do najczęściej występujących MSA należą antysyntetazy. Skierowane są przeciwko enzymom katalizującym reakcję wiązania aminokwasu do odpowiedniego tRNA. Antysyntetazy są markerami immunologicznymi tzw. zespołu antysyntetazowego. Jest to jednostka rozpoznawana od dość niedawna, charakteryzująca się występowaniem śródmiąższowej choroby płuc ILD, zapaleniem mięśni, w wielu przypadkach gorączką, *poliarthritis*, objawem Raynauda oraz charakterystycznymi zmianami skórnymi, jak ręce mechanika czy zmiany twardzinopodobne.