

**PW 21:
Inflammatory myopathies**

PW21-253	<p><u>ISCHAEMIA-REPERFUSION (I/R) INJURY IN THE PATHOGENESIS OF DERMATOMYOSITIS (DM): A MICROVASCULAR UNIT-BASED HYPOTHESIS</u> GITIAUX C¹, CHRISTOV C¹, BASSEZ G¹, DIMITRI D¹, AUTHIER FJ¹, GHERARDI R¹ (1) INSERM U841-E10 Neurosciences Department-IMRB- and Henri Mondor hospital, Creteil, FRANCE.</p>
To contact the author:: romain.gherardi@hmn.a php.fr.	<p>DM is considered as an humorally-mediated disease specifically targeting endomysial capillaries , but its pathophysiology remains uncertain. Recently, plamacytoid dendritic cells have been found in perimysium providing novel insights into immunopathologic reactions at work in DM (Greenberg et al, Neurology 2007; 69:2008-19). We made a reappraisal of DM-associated microvascular changes. Evidence of C5b-9 deposits (MAC) in muscle capillaries leading to capillary loss is a central finding in DM. It was initially regarded as the result of specific antigen-antibody recognition but, to date, no endothelial cell autoantigen has been identified in DM. Alternatively, MAC microvascular deposits may result from an ischaemia-reperfusion (I/R) injury, a situation characterized by 'no reflow phenomenon' which describes persistently reduced tissue perfusion after temporary artery occlusion, which is associated with local reactive oxygen species release, natural IgM and complement activation, capillary damage, and interstitial oedema formation (Weiser et al, J Exp Med 1996; 183: 2343-8). To substantiate the view that I/R, resulting from upstream arteriolar inflammatory changes, may account for MAC deposits and subsequent capillary depletion in DM, we first determined the number of capillaries fed by a single terminal arteriole (microvascular unit: MVU) in normal adult deltoid muscle. 3D reconstructions of 500 serial crossections immunostained for CD31 showed that terminal arterioles, roughly perpendicular to myofibers, fed multiples of 10, longitudinally oriented, capillaries. Then we analysed deltoid muscle biopsies of DM patients to assess spatial distribution of both MAC deposits (acute DM) and capillary loss, using multiple immunostainings, large tissue reconstructions and point-pattern analysis. Microvascular MAC deposition was either endothelial or abluminal (pericytic as suggested by αSMA immunostaining), and occasionally involved adjacent CD56⁺ satellite cells. Both MAC deposition and vascular depletion occurred in MVU-sized clusters of neighboring capillaries.</p> <p>We propose that I/R injury affecting individual MVU territories account for focal microvascular MAC deposition and depletion observed in DM.</p>

PW21-254	<p>CD8 T-CELL ENRICHMENT AND CD4 T-CELL DEPLETION OF MUSCLE IN DERMATOMYOSITIS PLONQUET A¹, BASSEZ G², GHERARDI RK², AUTHIER FJ² (1) Laboratoire d'Immunologie Biologique, CHU Henri Mondor, APHP, CRETEIL, FRANCE. (2) Centre de Reference GNMH, APHP; INSERM U841-E10, CRETEIL, FRANCE.</p>
<p>To contact the author:: francois- jerome.authier@hmn.ap hp.fr.</p>	<p>Dermatomyositis (DM) is a primary inflammatory myopathy, characterized by perifascicular fiber atrophy, complement-mediated microangiopathy, and B and T helper cell muscle infiltration. Recently, it was shown that muscle-infiltrating CD4+ cells in DM are mainly plasmacytoid dendritic cells (PDC), but not T helper cells. Moreover, a localized polymyositis-like immunopathologic process consisting of MHC-1-expressing fibers attacked by CD8+ T-cells may be occasionally observed in DM. These findings led us to reappraise muscle infiltrating T-cell phenotype in DM by using an innovative flow cytometry (FC) procedure.</p> <p>Ten DM patients and 22 controls with histologically normal muscle were included. Myopathological examination of biopsy samples included routine staining and immunolabelling of MHC-1, C5b-9, CD3, CD4, CD8, CD20, CD68 and CD56/NCAM antigens. Mononucleated cells (MC) were extracted from both muscle (MMC) and peripheral blood (PBMC) and subjected to FC to quantify CD3+, CD3+4+ (T helper), and CD3+8+ (T cytotoxic) cell subsets among leukocytes (CD45+). Calculation of muscle/blood (M/B) ratios for CD45+3+, CD3+4+ and CD3+8+ allowed detecting enrichment/depletion of muscle tissue in helper, cytotoxic, and total T-cells.</p> <p>In controls, CD3 M/B ratio was 0.93±0.22 (mean ± SD), CD4 M/B 0.94±0.31, and CD8 M/B 1.00±0.24. In DM, CD3 M/B was 0.85±0.24 (NS). CD4 M/B ratio was decreased (0.61±0.32; p<0.05), ranging from 0.30 to 1.35. In 8/10 DM patients, CD4 M/B ratio was below 0.8, the lower limit of the 95% confidence interval of controls. In contrast, CD8 M/B ratio was increased (1.94±0.40; p<0.05), ranging from 0.60 to 4.13. In 6/10 DM patients, CD8 M/B ratio was above 1.11, the upper limit of the 95% confidence interval of controls.</p> <p>In conclusion, our findings suggest that CD8+ T-cell-mediated cytotoxicity could occur in DM. Muscle CD4 T-cell depletion was consistent with recent data showing that, in DM, muscle CD4+ cells predominantly are PDC.</p>

PW21-255	<p><u>POLYMYOSITIS IN A HTLV1-POSITIVE CARRIBBEAN PATIENT : A CLINICOPATHOLOGICAL STUDY</u> LEBLANC A¹, BONDOIN L², MARCORELLES P², BLANCHARD C¹, ZAGNOLI F¹ (1) Service de neurologie Hôpital d'Instruction des Armées Clermont Tonnerre, Brest, FRANCE. (2) Service d'Anatomopathologie Centre Hospitalo Universitaire Morvan, Brest, FRANCE.</p>
<p>To contact the author:: fabien.zagnoli@orange.fr .</p>	<p>In polymyositis, CD8 cells recognise unknown antigen linked to HLA. But in some cases, this antigen can be identified.</p> <p>A sixty years old Caribbean woman complained for progressive walking disability for ten years, without pain. In 2007, physical examination revealed a limb girdle weakness with Gower's sign, thigh atrophy, but also left Babinski's sign and brisk reflex, but no spasticity. CK were at 1400 U/l (N< 190). CT scan showed asymmetric atrophy of quadriceps. Encephalic and medullar MRI were normal. There was hyperproteinorachia (0.53g/l). Muscle biopsy was performed on left vastus medialis and microscopic features were consistent with polymyositis. Mononuclear cell infiltrate was surrounding and invading non necrotic fibers. Most of the lymphoid cells were immunostained by CD8 antibody. This finding supports a cytotoxic mechanism. Because the association of myositis with a slight myelopathy in a Caribbean woman, an HTLV1 serology was performed and was positive in serum and CSF.</p> <p>Tropical spastic palsy has a wide spectrum from pure spastic myelopathy to proximal myopathy with some pyramidal signs, which is observed in 9% to 25%. This case highlights the association of the HTLV1 virus and a possibly induced polymyositis.</p> <p>Both polymyositis and inclusion body myositis have had been described associated with HTLV1 virus infection even if remaining extremely rare. Furthermore, Retrovirus have been suspected to initiate an autoimmune pathway leading to an inflammatory response and sometimes to a chronic degenerative process. Chronic persistent viral infection might be an initiating factor in the genesis of inflammatory myopathies.</p> <p>Corticotherapy can improve the disease but there is often a lack of efficiency after few months.</p> <p>As HIV, HTLV1 virus can induce myositis and serology must be performed in Caribbean patients or spouses of Caribbean men with polymyositis.</p>

PW21-256	<p><u>CLINICOPATHOLOGICAL AND MR SPECTROSCOPIC CORRELATION OF ADULT MYOPATHIES FROM A TERTIARY REFERRAL CENTRE IN INDIA</u> SINGH S¹, RATHORE C¹, GOYAL V¹, SHUKLA G¹, JAGANNATHAN N¹, BEHARI M¹ (1) ALL INDIA INSTITUTE OF MEDICAL SCIENCES, NEW DELHI, INDIA.</p>
<p>To contact the author:: singh_sumit@hotmail.com.</p>	<p>Background: Muscle histopathology, in myopathies does not give any information about the biochemical changes in the muscles in disease. MR spectroscopy can throw some light on the biochemical aspect of muscle pathology, and may be of incremental value in diagnosing various muscle diseases.</p> <p>Objective: To evaluate the role of in Vitro proton NMR spectroscopy in evaluating adult myopathies and to establish a clinicopathological and NMR spectroscopic correlation between various adult myopathies.</p> <p>Design/Methods: Adult patients with myopathy were subjected to a detailed clinical, electrophysiological, and histopathological evaluation and were then classified as having muscular dystrophy, inflammatory myopathies, mitochondrial myopathies, and indeterminate group. In vitro proton MR spectroscopy was performed in a subgroup of patients from each of the above groups and there NMR spectra analysed. A correlation was then attempted with the clinical picture of the patients, there histopathological group and the NMR spectra of the muscle biopsy specimens.</p> <p>Results: 77 adult patients were recruited in the study (58% muscular dystrophies, 18 % inflamatory myopathies, 12 % each mitochondrial and indeterminate group).Concentration of lactate was significantly increased in biopsies of patients with mitochondrial myopathies as compared to inflammatory myopathies and muscular dystrophies. Concentrations of alanine, glutamine, glucose and creatine were found to be significantly lowered in inflammatory myopathies and muscular dystrophies as compared to mitochondrial myopathies. Inflammatory myopathies showed significantly higher concentrations of glucose and creatine than patients with muscular dystrophies. MRS data also provided important diagnostic clues in six out of nine patients in whom no diagnosis could be established by traditional methods.</p> <p>Conclusions/Relevance: In vitro proton MR spectroscopy can be used as an adjunctive tool for evaluation of adult myopathies as it can indicate the spectroscopic differences between various subtypes of myopathies. In vivo studies can further establish its role in evaluation of myopathies.</p>

PW21-257	<p>INCLUSION BODY MYOSITIS INDUCED BY INTERFERON-ALPHA TREATMENT PÁL E¹, PFUND Z¹, SÜTÖ G², HORVÁTH G³ (1) Department of Neurology, University of Pécs, Pécs, HUNGARY. (2) Department of Immunology and Rheumatology, University of Pécs, Pécs, HUNGARY. (3) Department of Internal Medicine, Central Hospital of Interior Ministry, Budapest, HUNGARY.</p>
To contact the author:: endre.pal@aok.pte.hu.	<p>The 49-year old man's case is presented, whose medical history was unremarkable, until a hepatopathy was discovered 10 years ago. Serology and liver biopsy proved chronic hepatitis C virus (HCV) infection. In the first year interferon-alpha (IFNa) treatment (3x5 MU weekly) was started. In the last 7 years combined antiviral treatment (100 ug pegylated IFNa/week + ribavirin 1200 mg/day) was administered three times for 12 months. He became free of viruses (HCV RNA negative) after each treatment.</p> <p>Fatigue and generalized muscle weakness, difficulties in climbing stairs, standing from a chair, chewing and swallowing developed one year after the last treatment. At the admission mild weakness of hip extensors and flexors (4/5 MRC grade) was noted with normal trophic condition and absence of sensory abnormalities.</p> <p>Autoantibodies were negative including anti-nuclear, anti-dsDNA, anti-Jo1, anti-cardiolipin antibodies. HCV-RNA was negative in blood (RT-PCR). Needle EMG demonstrated myopathic changes in the deltoid and femoral rectus muscles. Biopsy of deltoid muscle showed marked myopathic changes with necrotic fibers, rimmed vacuoles and ragged red fibers. Marked endomysial infiltration with CD4 and CD8 lymphocytes was present. Sporadic inclusion body myositis (sIBM) was established and tapered immunosuppressive therapy was started. CK normalized and muscle strength was slightly improved.</p> <p>In our case sIBM was probably induced by IFNa and not by HCV, because sIBM developed after IFNa therapy and the patient's blood was free of viruses when myositis started.</p> <p>When symptoms of myositis develop after interferon therapy, not just the pathogenetic role of the basic disease, but also the possible role of the therapy-related autoimmune adverse reactions should be considered.</p>

PW21-258	<p>NECROTIZING MYOPATHY: AN IMMUNOPATHOLOGICAL REAPPRAISAL AUTHIER FJ¹, DIMITRI D¹, BASSEZ G¹, MOUTHON L², GUILLEVIN L², GHERARDI RK¹ (1) Centre de Reference GNMH, APHP; INSERM U841-E10, CRETEIL, FRANCE. (2) Departement de Medecine Interne, CHU Cochin, APHP, PARIS, FRANCE.</p>
<p>To contact the author:: francois- jerome.authier@hmn.ap hp.fr.</p>	<p>Necrotizing myopathy (NM) is an acquired condition histopathologically characterized by scattered necrotizing fibers at various stage of injury or healing (acute necrosis, myophagocytosis, basophilic fibers, centronucleation), with no or only minimal inflammation. NM usually was regarded as indicating a toxic or paraneoplastic origin. However, in number of patients, NM develops in the setting of autoimmunity and appears responsive to immunomodulatory drugs, leading myologists to delineate a new condition termed 'auto-immune NM' (AINM). However, in routine practising, the frontiers between AINM and polymyositis (PM) appear somewhat imprecise.</p> <p>We retrospectively evaluated patients with necrotizing myopathy diagnosed at Henri Mondor hospital between 2001 and 2007 according to muscle biopsy findings. Analyzed parameters included demographic data, associated conditions, CK levels and histopathological features, including immunohistochemical expression of MHC-1 (HLA-ABC) and -2 (HLA-DR), membranolytic attack complex (C5b-9), and PECAM/CD31 (endothelium).</p> <p>728 patients were diagnosed as inflammatory/dysimmune myopathy of which 39 (5.4%) had necrotizing myopathy (NM). Sex ratio (M/F) was 29/13, mean age 51 yrs (range 20-82). Cancer was found in 4/39 (10%) and autoimmunity in 21/39 (54%), including systemic sclerosis 8/39 (20%), interstitial lung disease 4/39 (10%) and anti-SRP antibodies in 3/39 (8%). Mean CK level was 15xN (range: 1-100xN). Abnormal myofiber expression of CMH 1 was found in 79% of patients and was ubiquitous in 24%. Focal myofiber expression of CMH 2 was found in 29%. C5b-9 deposition was observed on capillaries in 79%, myofibers in 61%, and both in 55%. When performed, PECAM immunostaining showed focal capillary loss (16/17).</p> <p>In conclusion, necrotizing myopathy most often corresponded to a dysimmune condition with immunopathological pattern ranging from pure AINM to probable PM, and characterized by local C5b-9 formation. Understanding the exact role of complement activation in myofiber injuries could be of first importance by opening promising tracks for further therapeutic strategies.</p>

PW21-259	<p>MACROPHAGIC MYOFASCIITIS-ASSOCIATED COGNITIVE DYSFUNCTION COUETTE M¹, BOISSE MF², GHERARDI RK³, BRUGIERES P⁴, CHEVALIER X², CESARO P², MAISON P¹, BACHOUD-LEVI AC¹, AUTHIER FJ³ (1) INSERM U841-Equipe 1, CRETEIL, FRANCE. (2) Pole Neurolocomoteur, CHU Henri Mondor, APHP, CRETEIL, FRANCE. (3) INERM U841-Equipe 10; Centre Reference GNMH, APHP, CRETEIL, FRANCE. (4) Neuroradiologie, CHU Henri Mondor, APHP, CRETEIL, FRANCE.</p>
<p>To contact the author:: francois- jerome.authier@hmn.ap hp.fr.</p>	<p>Macrophagic myofasciitis (MMF) is an emerging condition, characterized by specific muscle lesions assessing long-term persistence of aluminum hydroxide within macrophages at the site of previous immunization. Affected patients mainly complain of arthromyalgias, chronic fatigue, and cognitive difficulties. This study was designed to characterize the MMF-associated cognitive dysfunction (MACD) and to assess its specificity.</p> <p>Based on preliminary routine neuropsychological evaluation of 22 MMF patients, we designed a comprehensive battery of neuropsychological tests to prospectively delineate MACD. In a case-control study we included 12 consecutive patients with MMF at muscle biopsy and 12 control patients with rheumatoid arthritis (RA) and chronic pain. These control, matched for age, educational level, pain, fatigue and depression, were used to distinguish specific from non-specific cognitive impairment. Then, we ran a cohort study including a total of 25 patients to characterize MACD and test clinical factors could influence its severity.</p> <p>Compared to controls, MMF patients showed pronounced specific cognitive impairment. In the cohort study, all patients (100%) had measurable stereotyped cognitive dysfunction, mainly affecting (i) both visual and verbal memory; (ii) executive functions, including attention, working memory, and planning; and (iii) dichotic listening. Language and praxis were unimpaired Cognitive deficits did not correlate with pain, fatigue, depression, disease duration, or brain MRI abnormalities, and duration of pathological process did not influence their severity. They were suggestive of organic cortico-subcortical damage with deep white matter alterations. Pathophysiological mechanisms underlying MACD remain to be determined.</p>

PW21-260	<p>GRANULOMATOUS MYOSITIS MIMICKING INCLUSION BODY MYOSITIS LARUE S¹, MAISONOBE T², PAPO T³, CHAPELON-ABRIC C⁴, LIDOVE O³, SERVAN J⁵, VEBER H⁶, DASHI F¹, DUBOURG O²</p> <p>(1) Consultation de pathologie neuromusculaire, Groupe Hospitalier Pitie-Salpetriere, Paris, FRANCE. (2) Service de Neuropathologie, Groupe Hospitalier Pitie-Salpetriere, Paris, FRANCE. (3) Service de Medecine Interne, Hopital Bichat, Paris, FRANCE. (4) Service de Medecine Interne, Groupe Hospitalier Pitie-Salpetriere, Paris, FRANCE. (5) Service de Neurologie, Centre Hospitalier Rene Dubos, Cergy Pontoise, FRANCE. (6) Federation des Maladies du Systeme Nerveux, Groupe Hospitalier Pitie-Salpetriere, Paris, FRANCE.</p>
To contact the author:: odile.dubourg@psl.aphp.fr.	<p>We report four patients with chronic myopathy suggestive of inclusion body myositis (IBM), but in whom muscle biopsy showed a granulomatous myositis (GM). Our 4 patients, three women and one men, aged 71 to 83, presented with a slowly progressive and relatively selective weakness of quadriceps femoris. Asymmetric and selective atrophy of their forearms muscles was also noted in three of them with more severe involvement of the flexors than the extensors. CK levels were normal or slightly elevated. A diagnosis of inclusion-body myositis (IBM) was made before muscle biopsy. GM was found in all four muscle biopsy specimens. Evidence for systemic sarcoidosis was found in two patients. Corticotherapy was initiated in three patients and was associated with partial but significative improvement.</p> <p>The prevalence of granulomas in skeletal muscle biopsy specimens is low. Sarcoidosis is known as the single most commonly identifiable cause of it. For most experts, it remains unclear whether isolated granulomatous myositis (GM) really exists as a disease entity or only reflects how limited is the work-up to for sarcoidosis. Sarcoidosis have more severe proximal muscle involvement whereas distal myopathy is more commun in GM without sarcoidosis. This distinctive pattern of muscle weakness was not observe.d in our patients, who presented with a selective pattern of muscle involvement highly suggestive of IBM. Resistance to treatment with conventional forms of immunotherapy is one of the characteristic features of inclusion-body myositis. On the opposite, GM may be improved by corticotherapy. Although granulomatous inflammation is rarely found in muscle biopsy specimens and can easily be missed, its recognition is important from a prognostic and potentially therapeutic point of vue.</p>

PW21-261	<p><u>MRI VERSUS ULTRASOUND OR CLINICAL METHODS FOR SELECTION OF SITE FOR MUSCLE BIOPSY IN INFLAMMATORY MYOPATHIES - A RANDOMISED BLINDED TRIAL.</u></p> <p>SINGH S¹, AURANGABADKAR K¹, GOYAL V¹, SHARMA MC¹, SARKAR C¹, BEHARI M¹</p> <p>(1) All India Institute of Medical Sciences, New Delhi, INDIA.</p>
To contact the author:: singh_sumit@hotmail.com.	<p>Background –Muscle histopathology may be inconclusive because of the patchy muscle involvement in inflammatory myopathies. Imaging techniques may be of use in selecting the exact site for biopsy.</p> <p>Objective – To evaluate the role of muscle Magnetic resonance imaging, ultrasound in site selection for muscle biopsy in inflammatory myopathies, and to compare it with the conventional site for muscle biopsy.</p> <p>Material and methods – Patients with Inflammatory Myopathy from our neuromuscular clinic, were randomized for muscle biopsy to be done according to site selected by MRI or Ultrasound of the muscles of the thigh or from conventional site (right vastus lateralis muscle). All patients underwent MRI and USG and a skin marker indicated the site selected for biopsy. The muscle biopsy was performed according to the randomized group by a blinded investigator.</p> <p>Results – 29 patients with the diagnosis of IM were randomized for muscle biopsy into the MRI group (10 patients) USG group (10 patients) and conventional group (9 patients). Mean age of patients was 36.52 +/- 14.46 yrs. Clinical diagnosis was dermatomyositis in 8(27.6%) and polymyositis in 21 (72.4%) patients. Patients in the MRI group had a conclusive diagnosis in 100% cases, in the USG group in 90% cases and conventional group in 78% cases. Biopsy was inconclusive or normal in 3 patients –in the conventional or USG arm. Repeat biopsy in these patients, on the basis of MRI findings were suggestive of IM. The difference in the results of either arms were not statistically significant.</p> <p>Conclusion – MRI of the muscles is a sensitive test to select the exact site for muscle biopsy in patients with Inflammatory myopathies, superior to USG and conventional methods to select the site for muscle biopsy. Larger studies are required to further substantiate this finding.</p>

PW21-262	<p>CLINICAL AND ELECTROPHYSIOLOGICAL CHARACTERISTICS OF CHRONIC SENSORY ATAXIA ASSOCIATED WITH ANTI GD1B IGM ANTIBODIES</p> <p>UZENOT D¹, DELMONT E⁴, ATTARIAN S¹, VERSCHUEREN A¹, BOUCAUT J³, AZULAY JP², POUGET J¹</p> <p>(1) service de neurologie et de maladies neuromusculaires, CHU La timone, Marseille, FRANCE. (2) service de neurologie et de pathologie du mouvement, CHU La timone, Marseille, FRANCE. (3) service d'immunologie, CHU La conception, Marseille, FRANCE. (4) service de neurologie et de readaptation fonctionnelle, CHU L'archet, Nice, FRANCE.</p>
	<p>The objective of this study was to determine clinical, electrophysiological and biological characteristics of chronic sensory ataxia associated with anti-GD1b IgM antibodies. Anti-GD1b antibodies had been associated with acute and chronic sensory neuropathies. Place of these neuropathies among CANOMAD and CIDP is still discussed. We retrospectively studies patients presenting with chronic sensory ataxia in whom anti-GD1b antibodies were significantly elevated. 12 patients satisfied these conditions (6 men and 6 women, mean age 56 years). An electrophysiological examination and a CSF analysis were performed for all patients. Sera were tested for anti-GD1b, GQ1b, GM1 and anti-MAG antibodies. 11 of them were treated with at least one IVIg infusion.</p> <p>Six patients had anti-GD1b and anti-GQ1b IgM antibodies suggesting an antidisialosyl profile. They all had pure sensory symptoms and cranial nerve involvement in 4/6. Electrophysiology was suggestive of a ganglionopathy or a pure sensory neuropathy and was normal in one patient. These findings were suggestive of CANOMAD, but this syndrome was complete in only one patient. They all were treated by IVIg and 3/6 improved at least partially. Six patients had only anti-GD1b IgM antibodies. 4 patients had sensori-motor symptoms, whereas the two others had only sensory symptoms. Cranial nerve involvement was associated in 3/6. Electrophysiology was suggestive</p>

PW21-263	<p>THE PROGNOSIS OF ANTI-SYNTHETASE SYNDROME IS TO THE LUNG INVOLVEMENT</p> <p>STANCIU R¹, AMOURA Z¹, GUIGUET M², RIGOLET A¹, MUSSET L³, CAPRON F⁴, TOUITOU D⁵, CACOUB P¹, PIETTE JC¹, HERSON S¹, BENVENISTE O¹</p> <p>(1) Médecine Interne, Paris, FRANCE. (2) Biostatistique, Paris, FRANCE. (3) Immunobiochimie, Paris, FRANCE. (4) Anatomopathologie, Paris, FRANCE. (5) Radiologie, Paris, FRANCE.</p>
To contact the author:: olivier.benveniste@psl.a php.fr.	<p>Anti-synthetase syndrome is characterized by myositis, interstitial lung disease (ILD), arthritis, Raynaud's phenomenon, skin change of the hands (mechanic's hand), and the presence of autoantibodies of which anti-histidyl-transfer RNA synthetase (anti-Jo-1) is the most frequent.</p> <p>The aim of this retrospective study was to analyse the characteristics and outcome of 52 anti-Jo-1+ patients according to their clinical presentation and treatments.</p> <p>We describe 52 patients (13M/39F, median age: 41 y. [IQR, 32-53]). At diagnosis, 75% presented a proximal weakness (severe in 44%), 65% myalgia, 78% dyspnoea (> III or IV NYHA in 36%), 73% arthralgia (6% arthritis), 44% Raynaud's phenomenon (severe in 8%) and 17% mechanic's hands. Other signs were fever in 31% (> 38.5°C in 8%), weight loss in 11%, sicca syndrome in 35%. Their median CK level was 3575 U/ml [1188-8828] and CRP 19 mg/ml [6-58]. ANA titers were normal (< 1/80) in 45% or elevated \geq 1/320 in 30%. The most frequently associated ENA was anti-SSA (Ro52 and/or Ro60) in 62%. CT scan showed ILD in 77%. Pulmonary function tests showed median total lung volume (TLV): 64.5% [55-86], slow vital capacity (SVC): 68.5% [55-83], and CO diffusion capacity (CODC): 48% [39-58].</p> <p>All treated patients (49/52) received prednisone (1 mg/kg/day) during 4.5 y. [1.8-7.0], 9 in single therapy. For the 40 others, association with immunosuppressive drugs was needed. Overall, 21 treated patients were not ameliorated or worsened (3 deceased from their ILD), and 28 improved or recovered.</p> <p>Neither sex, age at onset, ANA titers, associated ENA, CK level, treatments nor their duration was associated with improvement under therapy. Patients who worsened presented higher value of CRP (p=0.003) and lower value of most pulmonary markers (TLV p=0.004, SVC p=0.015, CODC p=0.005).</p> <p>This study outlines the burden of chest involvement appreciated by pulmonary functional test for the prognosis of anti-synthetase syndrome.</p>

PW21-264	<p>MYOSITIS IN CHRONIC GRAFT-VERSUS-HOST DISEASE</p> <p>ARNE-BES MC¹, DELRIEU J¹, URO-COSTE E², CINTAS P¹, ATTAL M³</p> <p>(1) Service de neurologie et d'explorations fonctionnelles du système nerveux, Toulouse, FRANCE. (2) Service d'anatomie pathologique, Toulouse, FRANCE. (3) Service d'hématologie, Toulouse, FRANCE.</p>
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<p>To contact the author:: arne-bes.mc@chu-toulouse.fr.</p>	<p>Patients who have been treated with bone marrow transplantation and survived beyond 100 days often have chronic graft-versus-host disease (GVHD). Myositis or myopathy is usually rare in chronic GHVD. We report a 31-year-old woman who had myositis in the course of chronic graft-versus-host disease after allogeneic haematopoietic stem cell transplantation for acute lymphocytic leukemia.</p> <p>This woman was diagnosed as acute lymphocytic leukemia in 1990 at our hospital. She underwent chemotherapy and radiotherapy, benefited finally in 1995 from bone marrow transplantation and had in complete remission. Cyclosporin A and steroids had been given to prevent acute GHVD for several months.</p> <p>In 2005, the patient was admitted in hospital in a context of general fatigue, weight loss, abdominal pain with diarrhoea and myalgias. Also, she presented skin disease scleroderma-like. Muscular atrophy was noted in the 4 limbs but predominant in proximal muscles particularly in legs (quadriceps), the weakness was generalised but predominant in axial muscles almost cervical. These symptoms had deteriorated progressively.</p> <p>The patient had elevated levels of creatine kinase, liver enzymes were mildly increased. The most specific laboratory examinations revealed elevation of lactate dehydrogenase, aldolase, rate of antinuclear, anti-liver kidney microsomal and anti-mitochondrial antibodies. Electromyography found myogenic pattern in quadriceps, deltoid and in axial muscles. The muscle biopsy with histological and immunohistochemical study did not show typical histology of polymyositis. The diagnosis of late onset myositis, occurring 10 years after transplantation was established. The patient responded quickly to prednisone with clinical remission, levels of creatine kinase were reduced partially.</p> <p>In conclusion, we presented myositis which emerged in the course of chronic GVHD, probably caused by a cellular immune reaction of donor T cells.</p>
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<p>PW21-265</p>	<p><u>DYSIMMUNE MYOPATHY ASSOCIATED WITH ANTI-PL7 ANTIBODY SYNDROME UNDER COMBINED INTERFERON-ALPHA-2B/RIBAVIRIN THERAPY</u> AOUBA A¹, TERRIER B¹, GOULVESTRE C², GUILLEVIN L¹, AUTHIER FJ³ (1) Departement de Medecine Interne, CHU Cochin, APHP, PARIS, FRANCE. (2) Departement d'Immunologie, CHU Cochin, APHP, PARIS, FRANCE. (3) Centre de Reference GNMH, CHU Henri Mondor, APHP; INSERM U841-E10, CRETEIL, FRANCE.</p>
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<p>To contact the author:: francois- jerome.authier@hmn.ap hp.fr.</p>	<p>Muscle involvement in the setting of anti-threonyl-tRNA synthetase (anti-PL7) syndrome is usually regarded as similar to that associated with anti-Jo1 syndrome and roughly classified as polymyositis or dermatomyositis. Contrasting with this view, we report here a patient with anti-PL7 syndrome-associated muscle involvement, in whom extensive immunopathological evaluation of muscle injuries showed a peculiar pattern.</p> <p>An African 65-yrs HCV-infected woman was treated by peg-interferon (IFN)-alpha-2b (3 □g/kg/wk) and ribavirin because of increased liver fibrosis at FibroTest. Two weeks after treatment onset, she complained from marked flu-like symptoms and inflammatory arthromyalgias. After 24 wks, treatment was withdrawn but her condition continued worsening. Three months later, she presented with interstitial lung disease, arthralgias, painful proximal muscle weakness, fissured hyperkeratosis and weight loss. CK level was 7xN and CT scan showed interstitial pneumonitis. Muscle biopsy revealed an inflammatory myopathy characterized by (i) active myofiber necrosis process associated with ubiquitous major histocompatibility complex (MHC)-1 expression and membrane attack complex (C5b-9 complement component) deposition on sarcolemma; (ii) scattered endomysial macrophages and CD8+ T-cells; (iii) perivascular inflammatory infiltrates; and (iv) non-caseous granulomatous infiltrate, without giant cell formation. In addition, inflammatory process was associated with endomysial microangiopathy characterized by capillary loss and enlarged vessel lumen. Circulating antinuclear antibodies were positive (1/320), with specificity for threonyl-tRNA-synthetase (anti-PL-7 antibodies).</p> <p>Although clinical presentation was similar to anti-Jo1 syndrome, the histopathological pattern of muscle injuries notably differed. In particular, microangiopathy, sarcolemmal C5b-9 deposition and granuloma were not described in anti-Jo1 syndrome. Generally, we believe that histopathological pattern of muscle involvement associated with myositis-specific antibodies should be in depth reappraised in the light of modern immunopathology. In addition, in our patient, anti-PL7 syndrome developed under IFN-alpha-2b/ribavirin therapy, so pointing out the wide range of IFN-alpha-associated autoimmune disorders</p>
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<p>PW21-266</p>	<p>INFECTON AND ALTERATION OF HUMAN MUSCLE CELLS BY CHIKUNGUNYA VIRUS OR HTLV-1. DESDOITS M¹, HUERRE M², MOULY V³, RIVIERE JP⁴, BUTLER-BROWNE G⁵, GESSAIN A⁶, OZDEN S⁷, CECCALDI PE⁸ (1) Institut Pasteur, Unité EPVO, Paris, FRANCE. (2) Institut Pasteur, Unité Histotechnologie et Pathologie, Paris, FRANCE. (3) Université PM Curie, Institut de Myologie, Paris, FRANCE. (4) CHD Felix Guyon, St Denis de la Reunion, FRANCE. (5) Iniversité PM Curie, Institut de Myologie, Paris, FRANCE. (6) Institut Pasteur, Unité EPVO, Paris, FRANCE. (7) Institut Pasteur, Unité EPVO, Paris, FRANCE. (8) Institut Pasteur, Unité EPVO, Paris, FRANCE.</p>
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<p>PW21-267</p>	<p><u>ROLE OF REGULATORY T CELLS IN A NEW MOUSE MODEL OF EXPERIMENTAL AUTOIMMUNE MYOSITIS</u> SOLLY S¹, ALLENBACH Y¹, GRÉGOIRE S¹, DUBOURG O², SALOMON B¹, BUTLER-BROWNE G³, MUSSET L⁴, HERSON S⁵, KLATZMANN D¹, BENVENISTE O⁵ (1) CNRS UMR 7087, Paris, FRANCE. (2) Neuroanatomopathologie, Paris, FRANCE. (3) INSERM UMR787, Paris, FRANCE. (4) Immunochimie, Paris, FRANCE. (5) Médecine Interne 1, Paris, FRANCE.</p>
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Background: Polymyositis (PM) is a rare and severe inflammatory muscle disorders. Corticosteroids and other immunosuppressive drugs are partially efficacious and have many side effects. Regulatory CD4+CD25+ T cells (Treg) have been rediscovered as a pivotal cell population in the control of autoimmunity, but the role of Treg in PM has not been described.

Objectives: We aimed to develop a mouse model of PM to analyze Treg implication in the myositis development and, in particular, to provide the pre-clinical basis for future Treg therapy.

Methods: To develop Experimental Autoimmune Myositis (EAM), BALB/c mice were immunized 3 times, with 1 mg myosin emulsified in Complet Freund Adjuvant (CFA). Two weeks after the last immunization, muscle blocks are taken for immunohistology analyses. For Treg cells depletion mice were injected with anti-CD25+ antibodies. For Treg expansion CD4+CD25+CD62Lhigh Tregs were purified from spleen and lymph nodes by flow-cytometric cell sorting. Tregs were then cultivated in the presence of antiCD3 and antiCD28.

Results: All EAM mice developed a myositis with necrotic/regenerative fibers and endomysial inflammatory cells. Some fibers are also invaded. The infiltrates are composed by CD4+, CD8+ cells and macrophages. In Treg depleted mice, myositis was more severe (quantitative score of inflammation: 2.36 ± 0.9 vs. 1.64 ± 0.8 , $p = 0.019$). In opposite, injection of in vitro expanded polyclonal Treg ameliorated the disease (0.87 ± 1.06 vs. 2.4 ± 0.67 , $p = 0.047$). Besides, transfer of lymph nodes cells and sorted CD4+ cells from EAM mice induced a myositis in some of the irradiated recipients.

Conclusion: We can then produce consistent, reproducible and transferable EAM, aggravated by Treg depletion. The beneficial effect of in vitro polyclonal Treg injection is a first encouraging result regarding the therapeutic approach of the use of Treg for controlling myositis.

PW21-268

INJURED MUSCLE FASCIA: A FORUM FOR RESIDENT MACROPHAGES, EXSUDATE MONOCYTES, AND MONOCYTE-DERIVED DENDRITIC CELLS

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<p>To contact the author:: romain.gherardi@hmn.a php.fr.</p>	<p>Perimuscular connective tissue has been poorly investigated at the cellular level although several inflammatory myopathies may exhibit huge epimysial macrophage infiltration. We examined murine muscle connective tissue in steady state conditions and after an injury. Normal muscle epi/perimysium hosts a dense network of cells mainly composed of fibroblasts and resident macrophages (MPs). Flow cytometry and immunohistochemistry were in keeping with CD45+, CD11b+, F4/80+, CCR2+, and CD206+ resident MPs. After injury, epi/perimysium appeared as a privileged migration pathway for both ingressing and outgoing leukocytes, i.e. mainly monocyte/macrophages (MO/MPs).</p> <p>Using cross-bone marrow transplantation studies to discriminate resident from exudate MO/MPs, we observed that, rapidly after injury or exposure to TNF-alpha, muscle resident MPs concentrate above the injury site, and selectively release MCP1 and KC chemokines to attract circulating MO/MPs. Loss-of-function experiments were conducted in chimeric mice obtained by bone marrow (BM) transplantation, using Tg:CD11b-DTR mice as recipients and Tg:CAG-GFP mice as donors. In these chimeras diphtheric toxin (DT) injection induces selective resident MP depletion without involvement of circulating MOs. After myoinjury, selective resident MP ablation resulted in a dramatic attenuation of exudate MO/MP infiltration.</p> <p>From 1 to 3 weeks after myoinjury, regardless of its cause, another cell population derived from blood (CD11b+, CD11c^{int}, F4/80+) accumulated in the epi/perimysium. These cells were shown to present the antigen similarly to immature bone-marrow derived DCs in the allogenic mixed leucocyte reaction (MLR) assay, which consists in cocultures of the APC with allogenic immature T cells. By both their phenotype and their functional ability to present the antigen, these cells correspond to the recently acknowledged monocyte-derived DC subset.</p> <p>This study points out a critical role for resident epimysial MPs in orchestrating exudate MO/MPs infiltration, and documents de novo post-injury generation of immature dendritic cells which exact role in physiology and pathology deserves investigation.</p>
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<p>PW21-269</p>	<p><u>FUNCTIONAL TOLERANCE OF CD8+ T CELLS INDUCED BY MUSCLE-SPECIFIC EXPRESSION OF A NEO-AUTOANTIGEN IN TRANSGENIC MICE.</u> CALBO S¹, DELAGRÈVERIE H¹, ARNOULT C¹, AUTHIER FJ², TRON F¹, BOYER O¹ (1) Inserm U905, Rouen, FRANCE. (2) Inserm U841, Créteil, FRANCE.</p>
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The mechanisms of immunological tolerance to skeletal muscle autoantigens remains mostly unknown. To investigate this issue, we generated transgenic mice expressing the neo-autoantigen ovalbumin (OVA) exclusively in skeletal muscle (SM-OVA mice). SM-OVA mice were bred with OT-I or OT-II mice that possess a transgenic T cell receptor specific for OVA peptides presented by MHC class I or II, respectively. Hence, in this model, T lymphocytes are massively biased toward the recognition of OVA that is abundantly represented in muscle fibers. Both [SM-OVA x OT-I]F1 and [SM-OVA x OT-II]F1 appeared tolerant to OVA and no sign of muscle autoimmunity was detected. Tolerance to OVA did not involve clonal deletion nor anergy of T cells. We neither evidenced an increased regulatory T cell compartment. Rather, CD4⁺ T cell tolerance resulted from a mechanism of ignorance revealed by their response following OVA immunization. In marked contrast, CD8⁺ T cells exhibited a loss of their capacity to mount an OVA-specific cytotoxic response. This phenomenon was associated with up-regulation of the immunoregulatory programmed cell death-1 (PD-1) molecule. Adoptive transfer experiments further showed that OVA expression in skeletal muscle was required to maintain this functional tolerance. These results establish, for the first time, an asymmetric model of immunological tolerance to muscle autoantigens involving antigen ignorance for CD4⁺ T cells, whereas muscle autoantigens recognized by CD8⁺ T cells results in blockade of their cytotoxic function. These observations may be helpful for understanding the breakage of tolerance in autoimmune muscle diseases.

PW21-270

UNEXPECTED PATHOGENIC ROLE OF B LYMPHOCYTES IN A MOUSE MODEL OF INFLAMMATORY MYOSITIS

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Skeletal muscles do not physiologically express detectable levels of MHC class I while widespread appearance of MHC class I on the surface of muscle fibers is a hallmark of human autoimmune myopathies (myositis). Nagaraju *et al.* have developed a mouse model of myositis which consists in conditional up-regulation of MHC class I in skeletal muscle (named HxT), controlled by a Tet-off system. After MHC class I induction on skeletal muscle, mice develop clinical signs of muscle weakness, associated with muscle fiber degeneration and macrophage infiltration. Furthermore, roughly 30% of the animals produce Jo-1 antibody directed to histidyl-tRNA-synthetase, an autoantibody observed in a fraction of patients with myositis. Since the role of MHC class I is to present antigen to CD8 T cells and that CD8 T cells are the main immunological effectors in human polymyositis, it was thought that myositis in HxT mice was mediated by a CD8 T cell response to muscle autoantigens presented by transgenically-induced MHC class I molecules.

To address the role of the different lymphocyte subpopulations in the disease, we adoptively transferred cells from clinically sick HxT mice (provided by NIH) to B16 normal recipients. Surprisingly, only B cells could confer the disease, while CD4 or CD8 T cells, or even DC, did not. We have now confirmed these results by using T- and B cell-deficient Rag2 KO recipient mice. Therefore, B cells themselves are pathogenic in the absence of T cell help in Rag2 KO hosts.

These original observations may be clinically relevant since a growing number of case reports suggest a beneficial role of the B cell-depleting therapeutic antibody Rituximab in patients with refractory inflammatory myopathies (generally clinical forms associated to autoantibodies such as anti-SRP). The present model should provide clues to understand these immunological aspects.

