



TRANSFORMING CARE IN INFLAMMATORY AND AUTOIMMUNE DISEASES

Division of Rheumatology | 2014 Annual Report

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HOSPITAL
FOR
SPECIAL
SURGERY

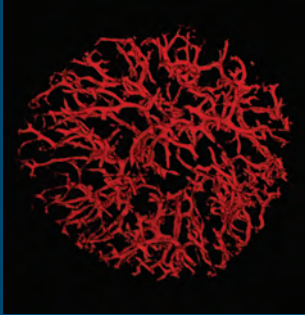
HOSPITAL FOR SPECIAL SURGERY



Founded in 1863, Hospital for Special Surgery (HSS) is a world leader in orthopaedics, rheumatology and rehabilitation. HSS is nationally ranked No. 1 in orthopaedics and No. 3 in rheumatology (in association with NewYork-Presbyterian Hospital) by *U.S. News & World Report* (2014-15). It is the first hospital in New York State to receive Magnet Recognition for Excellence in Nursing Service from the American Nurses Credentialing Center three consecutive times. Located in New York City, HSS also serves patients in the regional area with outpatient centers in Connecticut, New Jersey, Long Island, and Queens, and serves Florida patients with an outpatient rehabilitation office in South Florida. Patients choose to come to Hospital for Special Surgery from across the United States and from around the world. HSS has one of the lowest infection rates in the country. HSS is a member of the NewYork-Presbyterian Healthcare System and an affiliate of Weill Cornell Medical College and as such all Hospital for Special Surgery medical staff are faculty of Weill Cornell. The Hospital's Research Division is internationally recognized as a leader in the investigation of musculoskeletal and autoimmune diseases. To learn more please visit www.hss.edu.

ON THE COVER

Class V membranous lupus nephritis – a renal biopsy in a patient with SLE reveals an enlarged glomerulus with mild mesangial hypercellularity without significant endocapillary proliferation or major capillary wall abnormalities



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A MESSAGE FROM THE PHYSICIAN-IN-CHIEF AND CHAIR, DIVISION OF RHEUMATOLOGY



Dr. Mary K. Crow

I am pleased to report that during the past year the Division of Rheumatology has continued to make significant strides in the development, implementation, and further integration of patient care and clinical research initiatives, while strengthening our basic science component with the awarding of major grants from the National Institutes of Health and a number of foundations.

In 2013, more than 40,000 visits were made to our rheumatology practices and clinics. In addition, the Division of Perioperative Medicine, under the direction of Linda A. Russell, MD, provided pre- and post-surgical care of patients undergoing more than 29,000 surgical procedures. The co-management of patients by our rheumatologists, hospitalists, and orthopaedic surgeons is particularly important because so many who come to HSS for joint replacement are older, with co-morbidities such as hypertension, cardiovascular disease, diabetes, or other health issues that could preclude them from having surgery if not addressed. In the

five years since its establishment, the Division of Perioperative Medicine has developed into a model program gaining national recognition, and we congratulate Dr. Russell, who was recently named The Anne and Joel Ehrenkranz Chair in Perioperative Medicine at HSS. The endowed chair will support research in the field.

Expanding the Boundaries of Research

More than 50 studies involving the Hospital's rheumatologists were presented at the American College of Rheumatology annual meeting this past November. These ranged from laboratory-based studies of gene expression and alterations in cell signaling in lupus to novel collaborative studies of outcomes of joint replacement surgery in patients with rheumatoid arthritis or osteoarthritis. Our rheumatologists were also selected to present the latest information on pregnancy management in lupus patients, ethics in rheumatology, and challenges in the use of electronic health records.

With a well-established and vigorous program in basic research, we now continue to build the Division's infrastructure in clinical and translational research that will help facilitate both internal and external collaborations and expedite therapeutic advances for some of the field's most challenging

diseases. This effort progressed in earnest last year with the establishment of CATCH-US under the direction of Vivian P. Bykerk, MD, and this program will serve as a prototype of clinical research going forward.

CATCH-US is an outgrowth of the multicenter Canadian early Arthritis CoHort study begun by Dr. Bykerk and for which she served as principal investigator since 2006. The United States-based initiative includes a consortium of eight major medical center sites spanning the East and West Coasts. The ultimate goal of both endeavors is to personalize care for patients who have clinical, biochemical, and genetic predictors of poor prognosis and develop a tool that can guide the optimal selection of treatment strategies for these patients.

Dr. Bykerk is also playing a key role in the OMERACT (Outcome Measures in Rheumatology) RA Flare Group, which is developing a consensus-based definition of flare. Having the ability to identify and measure flare in patients is

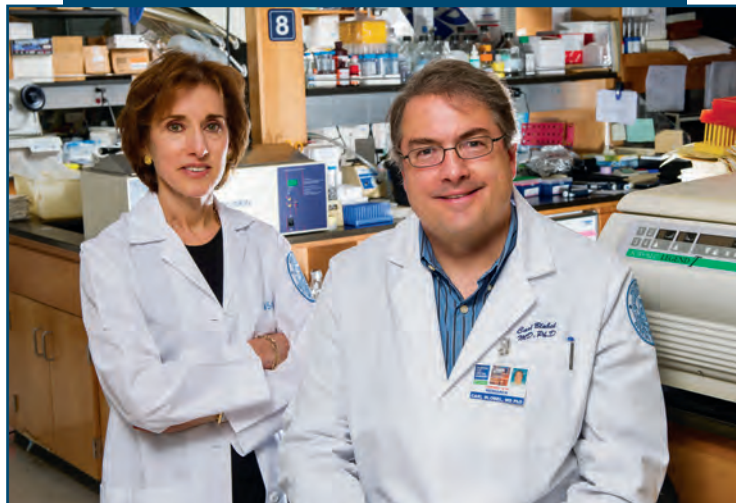
crucial for use in clinical trials, long-term observational studies, and clinical practice.

Most recently, our clinical research efforts received noteworthy recognition with the Hospital's selection as one of 11 sites nationally to participate in the Accelerating Medicines Partnership in Rheumatoid Arthritis and Lupus Network. The initiative brings together multidisciplinary research teams to analyze the interplay among biological pathways in tissues of patients with RA and lupus. The goal is to integrate data from multiple genome-wide analytic approaches to generate a comprehensive understanding of the mechanisms of tissue damage in RA and lupus and accelerate drug development. At HSS, studies will be led by Dr. Bykerk, Lionel B. Ivashkiv, MD, and Alessandra B. Pernis, MD [see article, page 5].

Important new partnerships have been created through the Alliance for Lupus Research and Pfizer's Centers for Therapeutic Innovation, which is supporting the research of Carl P. Blobel, MD, PhD, and Jane E. Salmon, MD, in their study of iRhom2, a new target for treatment of SLE, as well as my own work on the identification and validation of biomarkers associated with lupus flare. Pfizer's Centers for Therapeutic Innovation has a local biomedical research hub in New York City, enabling Pfizer and academic teams to work side-by-side to promote target discovery and drug development.

Dr. Bykerk, Susan M. Goodman, MD, and Lisa A. Mandl, MD, MPH, are collaborating with Boehringer Ingelheim on an observational study of novel immune modulating biomarkers in patients with ankylosing spondylitis and psoriatic arthritis to identify factors that can predict disease course and treatment response.

Funding for basic research scientists also continues to thrive. In February 2014, physician-scientist George D. Kalliolias, MD, PhD, was selected to receive the Sontag Fellowship in recognition of his advancement of promising research in rheumatoid arthritis. Dr. Kalliolias was chosen as this year's Fellow from a class of 15 researchers who received grants from the Arthritis National Research Foundation (ANRF), in partnership with The Sontag Foundation. ANRF grant recipients represent the top of a highly competitive field of young MD, PhD, and MD-PhD scientists at nonprofit research institutions across the country. Dr. Kalliolias' grant is entitled "TNF-alpha Modifies FLS Chromatin Landscape to Induce Disease State."



Dr. Jane E. Salmon and Dr. Carl P. Blobel

HSS SCIENTISTS RECEIVE RESEARCH AWARD FROM ALLIANCE FOR LUPUS RESEARCH AND PFIZER'S CENTERS FOR THERAPEUTIC INNOVATION

Carl P. Blobel, MD, PhD, Program Director of the Arthritis and Tissue Degeneration Program, and Virginia F. and William R. Salomon Chair in Musculoskeletal Research, and Jane E. Salmon, MD, Director of the Lupus and Antiphospholipid Syndrome Center, and Collette Kean Research Chair, have received a research award from the Alliance for Lupus Research and Pfizer's Centers for Therapeutic Innovation to study a new target for treatment of SLE.

Drs. Blobel and Salmon have previously identified the protein iRhom2 as a clinically relevant target for drugs to treat patients with rheumatoid arthritis. Blockade of iRhom2 could provide an effective and potentially less toxic alternative therapy to tumor necrosis factor-alpha blockers. The new research grant will enable Drs. Blobel and Salmon to extend their study of iRhom2 to the treatment of systemic lupus erythematosus.

Pfizer's Centers for Therapeutic Innovation (CTI) is a unique model for academic-industry collaboration, designed to bridge the gap between early scientific discovery and its translation into new medicines. CTI partnered with the Alliance for Lupus Research in 2012 to facilitate discoveries of new therapies for patients living with lupus. A key aspect of CTI is the close collaboration between Pfizer investigators and scientists at the funded academic centers, combining the research expertise of academics in disease biology, target identification, and patient populations with Pfizer's expertise and resources for drug development.

Theresa T. Lu, MD, PhD, received a two-year pilot award from the Weill Cornell Medical College Clinical and Translational Science Center (CTSC) to study “Targeting Dendritic Cells in Fibrosis,” as well as a new three-year grant from the Alliance for Lupus Research to study “Targeting a Dendritic Cell-Stromal Axis in Lupus” [see article, page 8].

Promoting Excellence in Rheumatology Education

In June 2014, Lindsay S. Lally, MD, graduated from the HSS Rheumatology Fellowship Program and was honored to receive the Distinguished Fellow Award from the American College of Rheumatology. On January 1, 2015, the Division will welcome Dr. Lally as a faculty member, with a plan to develop a practice in general rheumatology, with a particular focus on vasculitis. Dr. Lally will continue her research into the mechanisms and treatment of giant cell arteritis (GCA) that she began as a fellow. Having found increased levels of Rho kinase (ROCK) in the temporal artery biopsies of patients with GCA in a pilot study, Dr. Lally and Robert F. Spiera, MD, Director of the Scleroderma, Vasculitis, and Myositis Center at HSS, will now look at a larger number of biopsies to see if staining for ROCK activity is useful in enhancing the diagnostic potential of negative biopsies, and if ROCK may represent a novel therapeutic target. The findings may help identify patients who have GCA despite a negative biopsy for vessel inflammation, and prevent patients without GCA from getting unnecessary treatment with high doses of corticosteroids.

Dr. Lally epitomizes the success of our education and training programs in adult and pediatric rheumatology

directed by Anne R. Bass, MD, and Alexa B. Adams, MD, respectively.

With five highly focused Centers of Excellence, a diverse range of rheumatology clinics, and research programs directed by top physician-scientists across basic, translational, and clinical arenas, HSS

With five highly focused Centers of Excellence, a diverse range of rheumatology clinics, and research programs directed by top physician-scientists across basic, translational, and clinical arenas, HSS provides a rich training experience for our 13 rheumatology fellows.

provides a rich training experience for our 13 rheumatology fellows. Rheumatology fellowship training is further enhanced with the establishment of specialty clinics focused on inflammatory arthritis and on lupus, as well as a clinic devoted exclusively to the evaluation of new patients. A new primary care rheumatology clinic directed by rheumatologist Hendricks H. Whitman III, MD, is focused on the evaluation of clinical problems typically encountered in the context of primary care medical practices. Each of these clinics provides fellows with an opportunity to hone their clinical skills in the diagnosis and treatment of very challenging autoimmune and musculoskeletal diseases. In addition to our formal training programs, the HSS Rheumatology Academy of Medical Educators, led by Stephen A. Paget, MD, and Jessica R. Berman, MD, supports faculty and fellows through pilot grants for education research studies selected by an external peer review committee.

The *2014 Annual Report* of the Division of Rheumatology highlights many of our important research initiatives and clinical programs, which reflect the Hospital’s mission to ensure rapid application of scientific discoveries to patient care. On the pages that follow, you will learn about a few of the novel approaches that our faculty apply to challenging clinical questions and how they advance the care we provide to our patients.

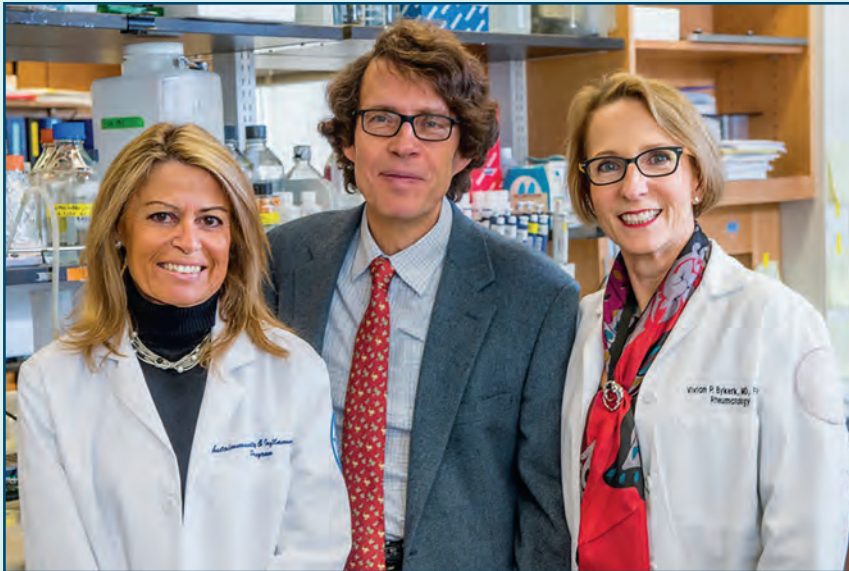


Mary (Peggy) K. Crow, MD, MACR
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Dr. Anne R. Bass

HSS Selected for Accelerating Medicines Partnership in Rheumatoid Arthritis and Lupus (AMP RA/Lupus) Network



Dr. Alessandra B. Pernis, Dr. Lionel B. Ivashkiv, and Dr. Vivian P. Bykerk

Hospital for Special Surgery is among 11 sites across the country selected by the National Institutes of Health to receive a research grant as part of the newly established Accelerating Medicines Partnership in Rheumatoid Arthritis and Lupus (AMP RA/Lupus) Network. Launched in February 2014, the NIH AMP Program is a public-private partnership developed to transform the current model for identifying and validating the most promising biological targets for the development of new drugs and diagnostics. The AMP RA/Lupus Network Leadership Center and Research Sites were selected through a competitive process, with first-year funding of \$6 million awarded in September.

The AMP RA/Lupus site at HSS is led by Vivian P. Bykerk, MD, Director of the Hospital's Inflammatory Arthritis Center; Lionel B. Ivashkiv, MD, David H. Koch Chair for Arthritis and Tissue Degeneration Research; Alessandra B. Pernis, MD, Peter J. Sharp Chair in Lupus Research; and Robert B. Darnell, MD, PhD, President and Scientific Director of the New York Genome Center. The investigators will focus on clinical research in RA and leverage unique cohorts of RA patients and a multidisciplinary team of clinicians and scientists at HSS, the New York Genome Center, and Mount Sinai Hospital at the University of Toronto to obtain paired samples of peripheral blood and synovial tissues from RA and control patients undergoing surgical procedures. HSS will contribute to the Network's efforts to identify molecular processes that distinguish

patients who experience flares of disease from those who do not, and RA patients who respond to specific drugs from those who do not.

"The NIH has brought together a network of experts to approach solving the mysteries of autoimmune disease in a novel way," says Dr. Bykerk. "Up until now the model has been an institution here, a scientific group there, who apply for a grant and come up with a finding. This is the first time that leaders in the field will look at how we can do this together. How can we get the right tissues from the right patients and understand what those

patients' disease course is in relation to what is being seen under the microscope and even in single cells? The plan is to have people collaborate to implement very new molecular technologies to understand signatures and targets in a way that has never been done before."

"These awards represent the first phase of an unprecedented approach to identify pathways that are critical to disease progression in rheumatoid arthritis and lupus," says NIH Director Francis S. Collins, MD, PhD. "Insights gained from this effort hold the promise of enhancing quality of life for patients and family members affected by these and other devastating autoimmune diseases."

Over five years, the AMP RA/Lupus Network will analyze the interplay among biological pathways, including at the single cell level, in tissues of patients with RA and lupus. The goal is to integrate data from multiple genome-wide analytic approaches to generate a comprehensive understanding of the mechanisms of tissue damage in these diseases.

"The Department of Rheumatology at HSS has a very capable group of clinicians and scientists who are able to integrate clinical and scientific research, and I think that will be a real asset to this collaboration," adds Dr. Bykerk. "Our hospital is uniquely positioned to contribute in a major way, and it is also very exciting to work with top researchers across the country to start to address the questions we all want to answer."

DEFINING THE PROBLEM OF OVERLAPPING RHEUMATIC DISEASES

How do you diagnose a rheumatic disease when the patient exhibits symptoms that appear to be related to lupus and, yet, they also have symptoms that signify rheumatoid arthritis? This conundrum occurs time and time again in rheumatology practice. It's a challenge for the physicians who have to determine and justify treatments. It's a frustration for the patients in their care who have to live with the uncertainty of their diagnosis. And it's a problem for healthcare institutions that must comply with precise diagnostic codes, myriad reimbursement regulations, and constricting best practice guidelines.

Michael D. Lockshin, MD, Director of the Barbara Volcker Center for Women and Rheumatic Disease at HSS and the immediate past Editor-in-Chief of *Arthritis & Rheumatism*, is one of the nation's preeminent experts in systemic lupus erythematosus, antiphospholipid antibody syndrome, and other autoimmune diseases. In his nearly four decades of clinical practice, Dr. Lockshin has seen more than his share of patients whose symptoms defy standard diagnostic criteria in a field that already encompasses some of the most challenging diseases in medicine.

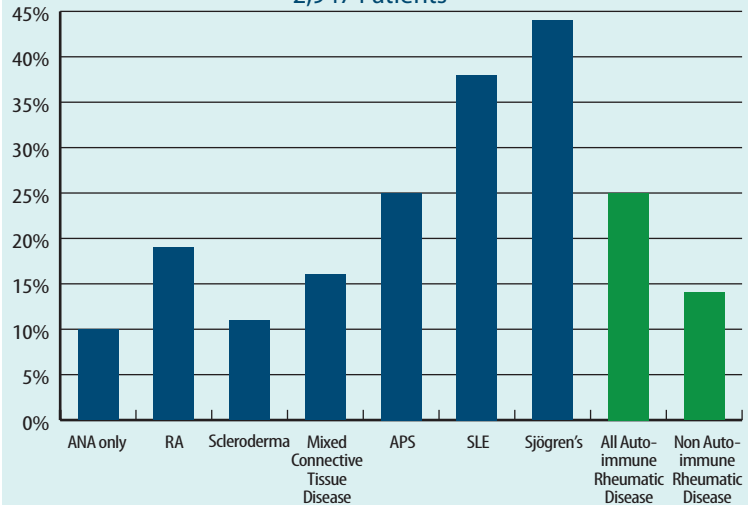
“When you are dealing with overlapping diseases, the concept of targeted therapy just explodes because aiming for one target in one diagnosis may be exactly the wrong thing to do for the overlapping diagnosis.”

– Dr. Michael D. Lockshin

“Traditionally, we characterize patients based on a diagnostic category – lupus, rheumatoid arthritis, scleroderma,” says Peggy K. Crow, MD, Physician-in-Chief and Chair, Division of Rheumatology. “In reality there are many patients whose symptoms overlap these categories. It's important for patients to know that these diagnoses are not so straightforward, and that it takes very expert, experienced rheumatologists to understand how to manage those who do not meet clear-cut diagnostic criteria.”

“Overlapping rheumatic disease is problematic on so many fronts,” says Dr. Lockshin. “They are ignored in basic science

Barbara Volcker Center for Women and Rheumatic Disease
Proportion of Patients With at Least One Overlap
2,947 Patients



studies and clinical trials. They are not recognized by ICD codes or best practice guidelines. This is a very important issue right now, with administrative, clinical, and research implications. The first priority is to recognize the problem, articulate it, and then dissect it.”

To obtain a better handle on the extent of the problem, Dr. Lockshin, Doruk Erkan, MD, MPH, Clinical Co-Director of the Mary Kirkland Center for Lupus Care, and Alana B. Levine, MD, reviewed nearly 3,000 patients followed by the Barbara Volcker Center for Women and Rheumatic Disease. “About 25 percent of these patients do not fit diagnostic guidelines, and they don't fit for several different reasons,” says Dr. Lockshin.

The most important of these, according to Dr. Lockshin, is overlapping disease, which can present in two ways: one in which patients have evidence of multiple diseases simultaneously, and one in which they have evidence of multiple diseases sequentially. “For example, patients can be in both categories where their diagnosis begins as lupus, and a few years later it looks like they have straight rheumatoid arthritis, and a decade later the diagnosis is back to lupus again.”

Further complicating the clinical picture of overlapping rheumatic diseases is that patients may have a co-occurring disorder such as Crohn's disease, multiple sclerosis, or diabetes. “These appear far more frequently than you would anticipate in patients with rheumatic illness and can interfere with what is regarded as best treatment practices,” notes



Dr. Alana B. Levine, Dr. Michael D. Lockshin, and Dr. Doruk Erkan

Dr. Lockshin. “There’s another group of patients who may be pregnant or have a medical issue such as cancer unrelated to their rheumatic disease. This could mean you can’t follow the treatment guidelines set for that rheumatic disease because if you do, you could harm the fetus or make a cancer worse.

“The issue of overlap disease is rarely if ever acknowledged, and it is very difficult to find any papers on how to treat these patients,” says Dr. Lockshin. “The papers are mostly descriptive, focusing on antibody associations or clinical features, and they do not consider mechanisms, discuss implications for therapy, and rarely mention outcomes.

“Between the 1960s and 1990s, the concept of treatment of the autoimmune diseases was to tone down inflammation and/or kill immune cells,” continues Dr. Lockshin. “To do this we used immunosuppressant drugs and the corticosteroids, which basically were sledgehammers to the immune system, very non-specific, and with bad side effects. More because of the side effects than because of the lack of efficacy, the decades that followed focused on developing targeted therapies. Instead of using sledgehammers, you could use scalpels, and you could get the disease under control with much less collateral damage. For example, the TNF-alpha inhibitors and similar agents are aiming at very specific, very narrow parts of the illness. That’s a very valid and very efficacious treatment for someone who has a very clean, simple, and consistent-over-time illness. But it does not apply at all to the type of patients I’m talking about.

“When you are dealing with these diseases, the concept of targeted therapy just explodes because aiming for one target in one diagnosis may be exactly the wrong thing to do for the overlapping diagnosis,” adds Dr. Lockshin. “If we target mechanisms specific for disease A, and if those mechanisms are wrong for disease B, we may do more harm than good.”

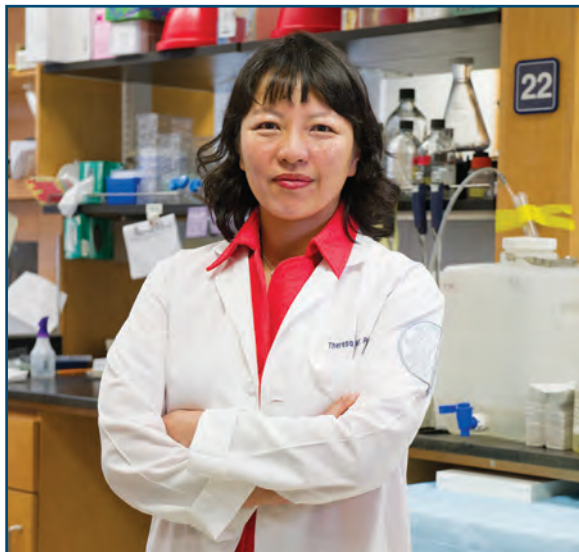
So from a scientific point of view, what are these diseases? From a clinical point of view, what do you do? And from an administrative point of view, what guidelines do you follow and what ICD codes do you use? “We really have to pay specific attention to patients with overlapping disease and separate them from those with pure diagnoses,” says Dr. Lockshin. “At the same time, we need to determine what they mean for the total picture of patients who come to rheumatologists. What do we do for them and how can we exclude them from the rules that we are being asked to follow?”

Questions for the Future

- Are the targets of overlap diseases the sum of the parts or something different?
- Do treatments targeted to the clinical/serologic/dominant phenotype help or hurt patients with overlap disease?
- What criterion/marker does one follow to measure response in overlap patients?
- What is the outcome of overlap patients?
- The Evidence Base: Do clinical trials (that exclude or ignore overlap) mislead?

TARGETING VASCULAR-STROMAL ISSUES IN IMMUNE FUNCTION

In the laboratory of Theresa T. Lu, MD, PhD, a pediatric rheumatologist and Associate Scientist in the Autoimmunity and Inflammation Program at Hospital for Special Surgery, the role of the vascular-stromal compartment in the regulation of immune cell activity within lymph nodes is a major focus of ongoing studies.



Dr. Theresa T. Lu

“This is a novel approach to autoimmunity. Rather than focusing on the immune cells, we are concentrating on the cells in the environment that support the immune cells.”
– Dr. Theresa T. Lu

“Lymph nodes are sites of immune responses, and, within lymph nodes, the activities of immune cells are supported and regulated by a highly plastic vascular-stromal compartment that can expand and undergo phenotypic alterations during immune responses,” explains Dr. Lu. “Blood vessels supply critical oxygen and micronutrients and fibroblastic stromal cells supply migration and survival cues, so manipulating the vascular-stromal compartment may be a means to manipulate immune function.”

According to Dr. Lu, the mechanisms that regulate vascular-stromal changes and how they contribute to the progression and regulation of the immune response are just beginning to be better understood. “Our past research has been to understand what occurs over time with an immune response as the lymph node grows,” says Dr. Lu. “What happens

to the vasculature? What happens to the fibroblasts? What are their dynamics, how do they grow, and how is this growth regulated?”

Through this earlier research, Dr. Lu and her colleagues were able to identify phases of vascular and fibroblast growth. More recently they determined that another phase follows that growth during which the vasculature stabilizes and returns to a state of quiescence. “This coincides with the timing for the generation of antibodies,” adds Dr. Lu. “We would like to understand how this re-establishment of quiescence impacts the antibody response.”

The researchers further demonstrated that the state of re-established quiescence is similar to the state found in a chronic autoimmune model. “This suggests that understanding of this phase in normal immunization models will allow us to better target the vascular-stromal compartment to disrupt autoimmune responses,” says Dr. Lu. “We are also testing the possibility that disruption of vascular quiescence could be a novel means by which to control pathogenic autoantibody generation. This is a novel approach to autoimmunity. Rather than focusing on the immune cells, we are concentrating on the cells in the environment that support the immune cells.”

Dr. Lu and her laboratory are now investigating a class of drugs – tyrosine kinase inhibitors – to see if they can disrupt the vascular-stromal compartment.

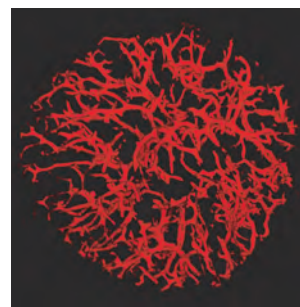


Image shows the blood vessels of a swollen lymph node. Diseases such as systemic onset juvenile arthritis are characterized by swollen lymph nodes, and Dr. Theresa Lu is studying the process that controls the lymph node and lymph node vascular growth.

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Chyou S, Tian S, Ekland E, Lu TT. Normalization of the lymph node T cell stromal microenvironment in lpr/lpr mice is associated with SU5416-induced reduction in autoantibodies. *PLoS ONE*. 2012. 7:332828.

RHEUMATIC MANIFESTATIONS OF ENDOCRINE DISEASE

“When patients come to see us with complaints of joint pains or what they consider might be arthritis, one of the first things we consider is what illnesses in internal medicine the patient’s symptoms could represent other than discrete rheumatoid arthritis or other rheumatic disease,” says Joseph A. Markenson, MD, MACR. “Several years ago, I became particularly interested in endocrine diseases as their manifestations tend to overlap with those in rheumatology. Endocrine patients can present with certain types of joint complaints. They can have the same positive blood tests that we see in arthritis.”

Accordingly, Dr. Markenson and Soumya D. Chakravarty, MD, PhD, FACP, a former HSS rheumatology fellow, began to take a closer look at rheumatic disease manifestations that might initially present in endocrine diseases or develop sometime during the progress of an endocrine disorder – the result of which is a comprehensive review article published in *Current Opinion in Rheumatology*. “We looked at the gamut of endocrinopathies that we see, with thyroid disease among the most common. People who have low thyroid may originally come in because they have stiffness of their hands or their knees in a symmetrical fashion, which looks very much like rheumatoid arthritis. But on further examination, their blood test results are different than those you see with RA. A diagnosis of endocrine disease can be further obscured because they may not always present with overwhelming hypothyroidism, slurred speech, weight gain, and other likely symptoms.”

Dr. Markenson points to carpal tunnel syndrome as an example. “There are five or six diseases that can present with carpal tunnel syndrome,” he says. “These include diabetes, rheumatoid arthritis, hyperparathyroidism, and thyroid disease. Every now and then a patient comes in with carpal tunnel and the differential leads you to think about thyroid disease. In addition, patients can present with pseudogout,

which can also mimic a symmetrical type of arthritis. Again, as rheumatologists, we have to be open to another way of looking at symptoms that may present as one illness, but be concealing another.”

In their article, Drs. Markenson and Chakravarty provide an update on the recent literature, covering the pathophysiology, genetic, and clinical findings on the association of

endocrine diseases and musculoskeletal complaints. “Each endocrine disorder has its own set of musculoskeletal ailments that can often mimic or present as definitive rheumatic diatheses, such as calcium pyrophosphate dihydrate deposition or diffuse arthralgia,” says Dr. Markenson. “In looking at the various endocrine disorders, both thyroid disease and diabetes have a number of rheumatic manifestations. However, with diabetes, patients usually develop a musculoskeletal problem after the diabetes appears. With thyroid abnormalities, patients present initially with achiness and muscle weakness, and can even have a positive ANA test. In looking at these diseases from various angles, we also found a lot of evidence of overlap. There appears to be a percentage of people with rheumatoid arthritis and lupus who have a higher degree of thyroid disease than the general population.”

The information is particularly valuable in the teaching of medical residents and rheumatic disease fellows, notes Dr. Markenson. “It’s important for them to recognize what other diseases should be considered in the differential diagnosis even if a patient presents first with a rheumatic complaint. Both rheumatologists and primary care internists should be skilled in identifying the manner in which muscles, tendons, ligaments, and joints are affected by diseases of the endocrine system.”



Dr. Joseph A. Markenson

KEY POINTS

- Endocrine disorders can initially present or manifest during the course of rheumatic diseases with a multitude of musculoskeletal complaints.
- Endocrine manifestations of underlying autoimmune disorders can occur commonly and need to be promptly recognized.
- Advances in genetic analyses through genome-wide association study (GWAS), as well as an emerging understanding of the effects of nonbiologic/biologic disease-modifying antirheumatic drugs (DMARDs) on endocrine manifestations in autoimmune diatheses, can potentially guide clinicians in selecting targeted, appropriate therapies in the future.

Source: *Current Opinion in Rheumatology*, January 2013.

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A COLLABORATIVE APPROACH TO LUPUS NEPHRITIS

Twice a year on a Friday, Kyriakos A. Kirou, MD, DSc, Clinical Co-Director of the Mary Kirkland Center for Lupus Care and Director of the Lupus Nephritis Program at Hospital for Special Surgery, and other HSS rheumatologists are joined by nephrologists and a renal pathologist from NewYork-Presbyterian/Weill Cornell Medical Center for the express purpose of an in-depth discussion of the care of challenging cases of patients with lupus nephritis, their optimal therapy, and outcomes. Discussion of lupus nephritis cases continues, less formally, every Friday, and literally at any time there is a need to do so, especially when rheumatology fellows need advice with their cases.



Dr. Kyriakos A. Kirou

“We established the Lupus Nephritis Program to allow us to focus specifically on this disease because it’s complicated and it requires a multidisciplinary approach,” says Dr. Kirou. “Our goal is to provide the best possible care for our lupus nephritis patients by using the exceptional resources available to us at Hospital for Special Surgery and NewYork-Presbyterian/Weill Cornell. Our approach includes the close collaboration of rheumatologists, nephrologists, a kidney pathologist, our nurse practitioner, and infusion room nurses.”

In addition to many other complications of lupus – including cardiovascular, pulmonary, musculoskeletal, gastrointestinal, and neuro-psychiatric – lupus nephritis is a prominent feature of the disease. “Approximately half of lupus patients develop lupus nephritis, usually early in the course of SLE,” says Dr. Kirou, “and approximately 10 to 20 percent of those will progress to dialysis or transplantation.

“When the kidney is affected, a very common finding is swelling of the feet,” explains Dr. Kirou. “Blood pressure can be high, which can cause headaches. And in a minority of patients, the urine becomes dark signifying the presence of blood, or foamy because protein is present. These are all clues for the rheumatologist to consider that the patient may have nephritis.”

Dr. Kirou notes that as the disease becomes more active, the patient may have a high ANA titer and a positive anti-double-stranded DNA test. “The levels of complement proteins C3 and C4 are often low, especially in lupus nephritis, reflecting the activation of the immune system,” explains Dr. Kirou. “Below 90 mg/dl for C3 and below 16 mg/dl for the C4 are considered low, but the lower they become, the more likely they are to be indicative of severe disease.”

While symptom presentation and laboratory tests can indicate a diagnosis of lupus nephritis, Dr. Kirou notes that renal ultrasound may be recommended to first rule out other causes of kidney disease. A kidney biopsy is then typically performed on all patients with clinical evidence of previously untreated active lupus nephritis.

“The biopsy will allow us to determine the degree of activity, the degree of inflammation in the kidney, and the degree of scarring,” says Dr. Kirou. “If a lot of scarring is present but not much disease activity, then we generally do not recommend immunosuppressant medications since there’s little or no room for improvement. These patients will likely go on to need hemodialysis or kidney transplant. Patients who are active on the biopsy will need aggressive therapy. The biopsy also helps us decide what therapy to administer. Our renal pathologist, Dr. Surya Seshan, reads the biopsies of all of our patients and helps us arrive at the right diagnosis and then the right treatment approach for each patient.”

Classifying and Treating Lupus Nephritis

A kidney biopsy also enables the lupus nephritis to be classified according to the International Society of Nephrology/Renal Pathology Society 2003 Classification of Lupus Nephritis and evaluated in terms of its activity and chronicity. The biopsy can also help exclude other causes for the renal disease such as acute tubular necrosis due to medications or hypovolemia.

“Class I represents very minor involvement of the kidneys and is not significant clinically. Class II also indicates a very mild degree of disease, with some inflammation present but not enough to trigger therapy,” explains Dr. Kirou. “The disease becomes more serious with Class III and Class IV,



(From left) Surya V. Seshan, MD, kidney pathologist, Miriam Chung, MD, and James M. Chevalier, MD, nephrologists, and Kyriakos A. Kirou, MD, DSc, and Doruk Erkan, MD, MPH, rheumatologists, during a weekly conference of the Lupus Nephritis Program

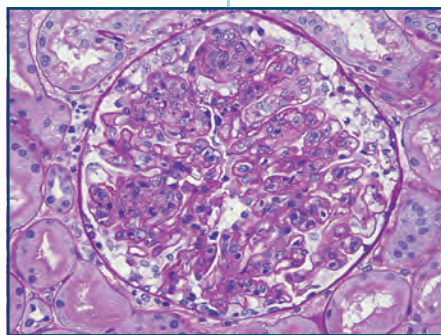
representing the proliferation of cells within the kidney or other cells coming from blood into the kidney, which will eventually cause trouble with scarring and kidney function.”

Class V may exist by itself or in association with Classes III and IV and is different than those. “With Class V, lupus nephritis is a membranous disease,” says Dr. Kirou. “So now the problem is in the basement membrane where the glomerular capillaries – small blood vessels where blood filtration to form the urine takes place – are attached. This Class V lupus nephritis, or membranous nephritis, can be mild or more severe depending on the amount of protein leaking into the urine. Classes III, IV, and V often require aggressive treatment. Most doctors will use steroids or similar compounds because they work quickly. The treatment may begin with a high dosage administered intravenously for one to three days just to get a head start on attacking the inflammation. This would be followed by an oral regimen of about 40 to 60 mg of prednisone per day.

“At the same time, we know that the prednisone doesn’t have a long-lasting effect so we will start an induction regimen with other agents to bring the disease under control,” says Dr. Kirou. “These would be classically either cyclophosphamide or mycophenolate mofetil. After we achieve some control, hopefully the disease will respond and we will start to see reduced swelling and a decrease in proteinuria and blood in the urine, as well as an improvement in blood pressure. When we reach that stage, we want to maintain it because if we don’t, the disease will come back. It’s a relapsing disease. So we will want to give a maintenance therapy for at least two years or so.”

Looking Ahead

Dr. Kirou recommends that in the immediate future physicians should be more sensitized to treating lupus nephritis very aggressively and very early on. “Time is kidney,” says Dr. Kirou. “It’s important to act quickly and effectively, especially to prevent scarring, which is irreversible. The more attacks there are on the kidney, the more likely the patient will need dialysis.”



Kidney biopsy from a patient with Class IV lupus nephritis showing a glomerulus with narrowing/closing of the capillaries from an abnormal increase of cells within those vessels. (Courtesy of Dr. Surya V. Seshan, Professor of Clinical Pathology and Laboratory Medicine at Weill Cornell Medical College)

The work of Dr. Kirou and his colleagues at HSS and NewYork-Presbyterian extends to collaborations with rheumatologists and nephrologists with an interest in lupus nephritis across the country and around the world through organizations such as the Lupus Nephritis Trials Network. The mission of this international organization of clinicians and scientists is to foster collaborations that include clinical trials designed to prevent chronic kidney disease and end-stage renal failure in patients with lupus; develop

guidelines for assessing and treating patients with lupus nephritis; and pursue investigations on a wide variety of therapeutic agents, treatment methodologies, and biomarkers of disease.

Dr. Kirou is also an investigator in the ALLURE study, a Phase III randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of abatacept or placebo in combination with mycophenolate mofetil and corticosteroids in subjects with active Class III or IV lupus nephritis. The study is expected to enroll approximately 400 patients in 120 sites worldwide.

DISEASE-FOCUSED CENTERS: MODELS OF EXCELLENCE

In 2010, Mary K. Crow, MD, MACR, Chief of the Division of Rheumatology, created a “Centers of Excellence” framework to enhance the coordination of patient care, facilitate training and education programs, and to advance research initiatives focused on specific autoimmune and inflammatory disorders. In particular, these centers serve to stimulate the dialogue among the Hospital’s clinicians and scientists, who routinely collaborate to identify clinical challenges that can be explored and explained at the most basic level with a goal toward developing better therapeutic options for patients.

BONE HEALTH AND OSTEOPOROSIS CENTER OF EXCELLENCE

Linda A. Russell, MD, Director



Basic scientists and medical and orthopaedic specialists have come together in the Bone Health and Osteoporosis Center to focus on the prevention and treatment of osteoporosis, Paget’s disease, and related

bone disorders; preserving bone quality; and promoting bone healing. HSS physicians and nurses have developed a new clinical pathway to better identify those with bone disease and those at risk in order to map the course for proper intervention. The pathway is currently being used in candidates for spinal fusion surgery to optimize their bone health prior to and following surgery.

INFLAMMATORY ARTHRITIS CENTER OF EXCELLENCE

Vivian P. Bykerk, MD, Director



The Inflammatory Arthritis Center brings together the physicians who treat patients with rheumatoid arthritis, psoriatic arthritis, spondyloarthropathies, and other inflammatory disorders. Most recently, the Center launched CATCH-US,

an HSS-based, national multicenter program to study patients with new onset arthritis and develop approaches to improving diagnosis, treatment, and outcomes. In addition, the Hospital’s rheumatologists and orthopaedic surgeons have a number of research projects underway to explore and improve perioperative outcomes of patients with rheumatic disease.

LUPUS AND ANTIPHOSPHOLIPID SYNDROME CENTER OF EXCELLENCE

Jane E. Salmon, MD, Director



Hospital for Special Surgery is home to a renowned team of clinicians and scientists who are seeking to address the many challenges of systemic lupus erythematosus (SLE) and

antiphospholipid syndrome (APS), investigating the myriad manifestations of these diseases at the molecular level and bringing their findings to bear on managing SLE and APS and their complications in patients. Two decades ago, the Hospital became the nation’s first National Institutes of Health-sponsored Specialized Center of Research in SLE, and since then has made many contributions to identifying immune system triggers, understanding the role of interferon and other immune system mediators, and uncovering causes of disease activity and flares.

PEDIATRIC RHEUMATOLOGY CENTER OF EXCELLENCE

Thomas J.A. Lehman, MD, Director



Our pediatric rheumatology program has made great strides in the care of children with rheumatic diseases and related conditions, continuing to identify new and effective therapeutic treatments. Medications that are used

by adult rheumatologists are now prescribed, as appropriate, by our experienced pediatric rheumatologists with excellent outcomes. With new biologic therapies, many of them tested at HSS, along with physical therapy, children are regaining normal function and quality of life.

SCLERODERMA, VASCULITIS, AND MYOSITIS CENTER OF EXCELLENCE

Robert F. Spiera, MD, Director



Scleroderma is a major focus of basic research studies and clinical investigations at HSS. The Center’s physician scientists continue to collect clinical information and biological materials on patients with scleroderma

to learn more about the pathophysiology of the disease. They have been involved in a number of clinical trials to define better therapies for this population. Programs continue to grow in vasculitis following the Hospital’s participation in the landmark study of rituximab therapy, and in inflammatory myopathies, with a goal to increasing understanding of these rare diseases.

SURGICAL MANAGEMENT OF RHEUMATOID ARTHRITIS

Susan M. Goodman, MD

A young woman with long-standing rheumatoid arthritis came to HSS because of knee pain. She had undergone knee replacement surgery, as well as hip replacement surgery, 20 years prior. When she presented here she had relatively active disease but had developed dermal vasculitis as a complication of therapy with a TNF- α inhibitor, and was now being managed on a synthetic disease modifying drug (DMARD), methotrexate and high-dose prednisone. Upon admission, in addition to active disease, we found knee swelling and loosening of the implant as indicated by radiographic osteolysis. She also had cervical spine instability. We elected to perform knee replacement revision surgery. We were able to exclude infection both with preoperative cultures, and cultures and histopathology of the operative specimen. Once her wound healed we put her on a different biologic DMARD, and she has done extremely well.

As a member of the Hospital's multidisciplinary Surgical Arthritis Service and Medical Chief of the Combined Arthritis Program (CAP), rheumatologist Susan M. Goodman, MD, has long been involved with the management of patients with complex rheumatic diseases undergoing orthopaedic surgery. "The surgical management of these patients is influenced by many factors associated with their disease," says Dr. Goodman. "Through CAP, we work closely with the orthopaedic surgeons to take care of these complicated patients."

According to Dr. Goodman, one of the characteristic features of the patient with rheumatoid arthritis who is undergoing orthopaedic surgery is the high likelihood that they have cervical spine involvement. A study of patients with RA awaiting arthroplasty found that almost half had cervical spine involvement that was radiographically detectable," says Dr. Goodman. "Comparing this to another study looking at general surgery patients with RA, only 20 percent had evidence of significant cervical spine involvement. Clearly, the patients with erosive peripheral arthritis are more likely to have destructive cervical spine disease as well. For these patients, we very simply take a flexion extension X-ray of the neck, which brings out any instability. If we see anything concerning, we will order an MRI of the spine to determine the significance of the instability.



Dr. Susan M. Goodman

"Although this particular patient did have subluxation of the spine, it wasn't of a degree that would preclude performing the surgery safely," continues Dr. Goodman. "We worry because the neck can become manipulated if someone is undergoing general anesthesia. While most of our surgeries are done under regional anesthesia, occasionally with these complex patients there is a need to intubate, and in that case you really want to know their anatomy in advance."

One of the most important considerations in the perioperative management of patients with RA is balancing wound healing and infection risk against ongoing disease control and their ability to participate in postoperative rehabilitation routines. Lowered immunity due to drug therapy heightens the concern for postoperative infection and delayed wound healing. "One of the concerns we have in patients coming in for orthopaedic surgery is what to do about their medications," explains Dr. Goodman. "TNF- α is a critical chemical mediator in fighting infection. So targeting the immune response with TNF- α inhibitors means that we lose some of our ability to fight infection, particularly when an artificial joint prosthesis is implanted. Through observational data from registries looking at the risks associated with TNF- α inhibitors, we know that while the increase in risk of infection is greatest within the first six months of starting a TNF inhibitor, the risk might be similar to the risk in any patient with active RA who initiates DMARD therapy.

"There are clearly contextual factors that have to do with severity of disease, activity of disease, and other factors such as smoking

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Surgical Management of Rheumatoid Arthritis

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or glucocorticoid use, as well as arthroplasty itself, which are also risk factors for infection. Our current standard, which is in line with the recommendations of the various rheumatology associations, is to stop the TNF- α inhibitors approximately one to four weeks prior to surgery. Methotrexate and similar drugs, however, appear safe to use at moderate doses through surgery. Patients who remain on methotrexate do much better. They have, in fact, fewer complications, no flares, and recuperate quite well.”

Cardiac involvement is also a major consideration preoperatively in patients with RA. Studies done at HSS have demonstrated that the underlying risk of cardiac disease is much higher in RA patients. The occurrence of significant vascular stiffening is one way to measure likelihood of risk and that degree of risk increases with disease activity. “This seems to be a factor associated with poorly controlled RA,” notes Dr. Goodman. “In other studies we’ve done, however, we have seen that the likelihood of patients coming in for knee or hip replacement having had a preexisting myocardial infarction was no higher than patients with osteoarthritis. More importantly, when we looked at those patients that do undergo surgery for RA, the number of patients who had cardiac complications was no greater than the OA patients. We thought it would be, based on the known increase in atherosclerotic vascular disease in patients with RA, suggesting our screening has been successful.”

Dr. Goodman and her colleagues continue to pursue important studies regarding total hip and total knee replacement surgery for patients with RA and other autoimmune diseases. They are currently in the planning stages for a study that will look at RA flares after total hip and knee replacement surgery, and arthroplasty outcomes one year later. “We will be able to analyze in very careful detail if the patients who flare tend to have a worse outcome compared to those patients whose disease remains under control, and if the arthroplasty outcome is related to their overall disease activity,” says Dr. Goodman. “This will also give us the advantage of prospectively gathering biologic specimens so we can understand the biology of flare as well.”

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MEETING THE CHALLENGES OF SYSTEMIC SCLEROSIS

Jessica K. Gordon, MD

A 42-year-old male with a history of testicular cancer that was treated and cured developed puffiness of his hands and Raynaud’s phenomenon a year later. The patient then developed thickening of the skin, especially of the hands, that restricted his range of motion and ability to use his hands. The skin thickening moved up the arms and to the chest and other areas of the body. Soon after, he was diagnosed with systemic sclerosis. He’s now had the condition for a few years and in that time he developed inflammatory arthritis, interstitial lung disease, cardiomyopathy, and ventricular tachycardia requiring implantation of a pacemaker. During this period of illness, the patient relocated to New York and was referred to Jessica K. Gordon, MD, at HSS. The patient has been treated with various immunosuppressive medications and the addition of a pacemaker, which have provided some improvement with his skin, level of pain and mobility, stability in his lungs, and a better ejection fraction.

“The treatment of systemic sclerosis is a challenge for several reasons,” says Jessica K. Gordon, MD, a rheumatologist with the Scleroderma, Vasculitis, and Myositis Center of Excellence directed by Robert F. Spiera, MD. “The disease is heterogeneous. Organ system involvement varies from patient to patient and so does clinical course and response to treatment. The fibrotic manifestations of the disease, including interstitial lung disease and skin disease, can be resistant to treatment with immunosuppressive medicines. These are some of the reasons why further research into this disease and its treatment are so important.”

Currently, there is no medication specific for the treatment of scleroderma that is FDA approved. “In that sense, every medication that we use is ‘off label,’ although several of the manifestations of scleroderma are not unique to scleroderma,” says Dr. Gordon. “In some patients we see inflammatory arthritis or inflammatory myopathy, which we see in several rheumatic diseases. Because these different manifestations share some common pathogenetic features, we typically use immunomodulatory medicines to treat other aspects of scleroderma as well.”

Dr. Gordon notes that scleroderma is less common in men – about 20 to 25 percent of cases – and may be more severe. “Another interesting aspect of this case is that the patient had a diagnosis of cancer before his scleroderma diagnosis,”



Dr. Jessica K. Gordon

says Dr. Gordon. “Recently a whole body of work has appeared that has shown a link between scleroderma and malignancy in a subset of patients. That malignancy link can happen before, at the same time, or following the diagnosis of scleroderma. There may be an immunologic response to a tumor that triggers the onset of the scleroderma.”

Dr. Gordon’s clinical insight in scleroderma is supported by a vigorous research program. She and Dr. Spiera conduct a range of observational studies that are based in the Hospital’s scleroderma patient registry, as well as a number of clinical trials. These include the multisite Prospective Registry of Early Systemic Sclerosis observational study and an HSS single-center pilot trial looking at the use of belimumab, an FDA-approved treatment for lupus that they are evaluating in the scleroderma population. “This is the first study to look at that medication in scleroderma,” notes Dr. Gordon. “We are using it in combination with mycophenolate mofetil, so that all patients receive this medication, and others are randomized to receive either belimumab or placebo. We are also starting to collaborate with other sites to help foster efficiency in recruiting for trials in a rare condition like scleroderma.”

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CARING FOR THE CHILD WITH POLYARTICULAR ARTHRITIS

Alexa B. Adams, MD

A 7-year-old girl was seen in follow-up after a recent hospitalization for joint and neck pain. She had a several month history of wrist pain and swelling, but had more recently developed worsening neck pain prompting hospital admission. In the hospital, pediatric rheumatology and neurosurgery were consulted and she was diagnosed, on the basis of imaging studies and laboratory testing, with polyarticular juvenile idiopathic arthritis. There were multiple joints involved at diagnosis: joints of the cervical spine, one elbow, both wrists, and one knee. There was significant limitation in motion of the right wrist and left elbow, as well as the neck. She experienced daily pain and morning stiffness interfering with her activities.

Review of outside wrist imaging confirmed synovitis. CT and MR imaging of the cervical spine confirmed cervical spine involvement consistent with an inflammatory arthropathy. She was found to be rheumatoid factor and anti-CCP (citric citrulinated peptide) antibody positive. Her markers for inflammation were elevated suggesting ongoing disease activity. The family expressed concerns about their daughter’s prognosis, outlook for long-term functionality, and worry over potential medication side effects.

The patient required the combination of an anti-tumor necrosis factor α agent and subcutaneously administered weekly methotrexate to control her disease. With this combination therapy her markers of inflammation normalized, her neck pain, joint pain, and swelling subsided. She was able to resume her activities. Physical and occupational therapy allowed for a good improvement in the range of motion of her affected joints. The patient continues to be followed by neurosurgery for monitoring of her cervical spine involvement and appropriate restriction in her activities has been implemented. Ophthalmologic exams to date have revealed no evidence for inflammatory eye disease complicating her arthritis. She is currently growing and thriving in the fourth grade. She is followed closely by pediatric rheumatology for continued monitoring of her blood work and response to therapy.

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Caring for the Child with Polyarticular Arthritis

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Dr. Alexa B. Adams

“Juvenile idiopathic arthritis is not just one disease and has different presentations from patient to patient,” says pediatric rheumatologist Alexa B. Adams, MD. “Cases can vary significantly, and often this can be a diagnosis of exclusion. Children may present with swelling of the joints. Others will present with recurrent pain and stiffness and these patients can take longer to diagnose or to come to a rheumatologist for care. My job is to tease out why the child is in discomfort.”

Children with polyarthritis often require intensive therapy to control their disease, and it is clear that the sooner the diagnosis is made and appropriate therapy instituted the better a child is likely to do over the long term. “We are fortunate that there are now very effective therapies available for juvenile arthritis,” says Dr. Adams. “We use many of the same medications, including in the case of polyarticular juvenile idiopathic arthritis a combination of tumor necrosis factor-alpha (TNF- α) inhibitors and methotrexate, which are used in the adult inflammatory arthritis population but dosed according to the child’s body weight.”

Dr. Adams will discuss the expected risks and benefits of each new medication at length with the family. For example, in the case of TNF- α inhibitors, while they are an effective treatment for juvenile idiopathic arthritis (JIA), there is concern that they may increase infection rates. Active JIA may also render patients vulnerable to infection. A prospective study recently undertaken with HSS pediatric rheumatologists comparing infection risk and disease activity in children with JIA treated with and without TNF- α inhibitors suggested no difference in infection rates between the two groups.

Dr. Adams notes that care for children with arthritis extends beyond the pediatric rheumatologist, and a team approach clearly works to the benefit of the patient. “Communication

with the primary care physician is essential regarding immunizations and management of routine childhood illnesses,” she says. “Children with arthritis are at increased risk for developing inflammatory disease in their eyes. Because of this, whether or not they develop symptoms, they need to be regularly evaluated by ophthalmologists. Pediatric orthopaedists and multiple other specialists may also be involved in their care.”

Dr. Adams and her colleagues also work to educate schools about special accommodations that their patients may need in order to facilitate their successful return to academic life. “We partner closely with rehabilitation professionals to ensure that physical and occupational therapies are in place when needed,” she says.

Dr. Adams believes that her role lies not only in making the diagnosis and implementing appropriate therapy for her patient, but also in partnering with the family and other treating physicians to provide the best possible outcome.

“Juvenile idiopathic arthritis is not just one disease and has different presentations from patient to patient.”

– Dr. Alexa B. Adams

“It can be difficult for families to accept the diagnosis of a chronic condition and they have a number of concerns,” says Dr. Adams. “I always ask them to express exactly what those concerns are. Sometimes they are about the proposed therapies. Sometimes they are about whether their child will be able to continue to attend school and participate in activities the way that they always had. And sometimes they have other worries. Children and their families need a physician who will take the time to acknowledge, listen to, and discuss their concerns. Seeing my patients respond to treatment and resume school and activities with improvement in their arthritis symptoms is the most rewarding part of my job.”

Her patients and their families agree that Dr. Adams takes this to heart. In 2012, she was awarded the “My Doc Rocks” award from the Arthritis Foundation, nominated by a grateful mom of one of her young patients.

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Division of Rheumatology

2014 Annual Report

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SELECTED PUBLICATIONS

December 2013 - November 2014

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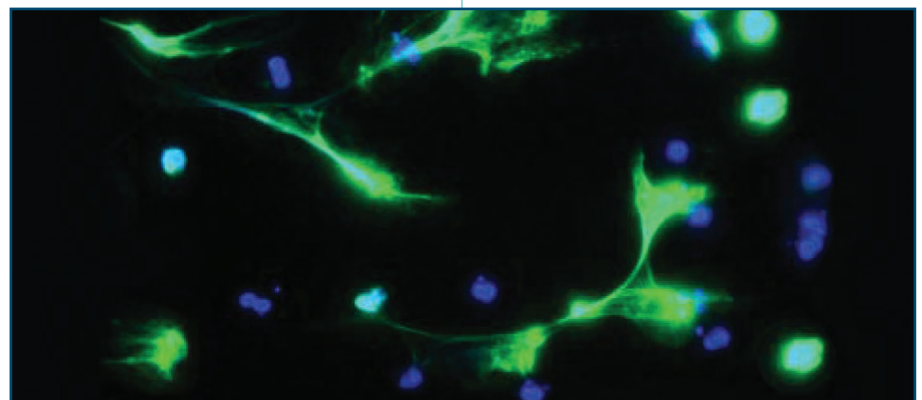
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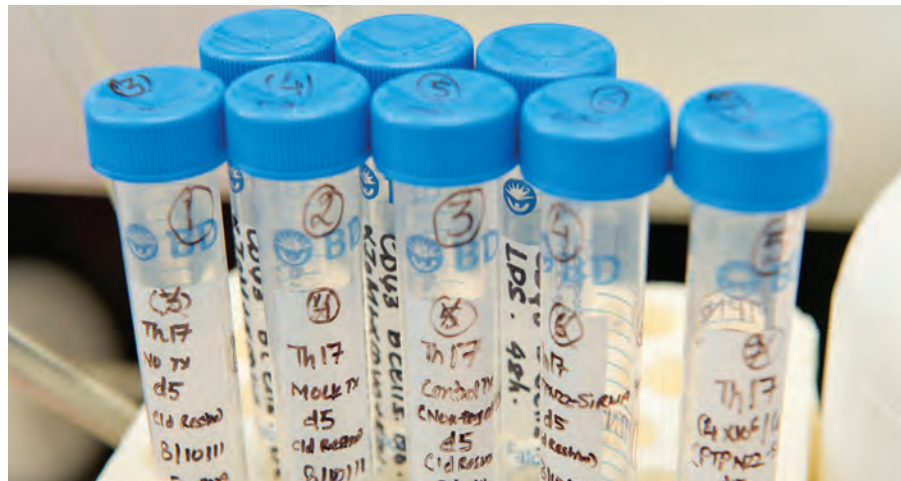
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