Annual Course Lecture ACL-1

Differential Diagnosis of Systemic Rheumatic Diseases Shoichi Ozaki

Division of Rheumatology and Allergology, Department of Internal Medicine, St. Marianna University School of Medicine, Kawasaki, Japan

Systemic rheumatic diseases (SRD), also called systemic autoimmune diseases or connective tissue diseases, develop through the interaction of genetic and environmental factors. This interaction breaks self-tolerance and induces autoimmunity and inflammation, which result in the damage of multiple organs including connective tissue such as joint, muscle and blood vessels. The key to the diagnosis of SRD is to suspect your patient to have SRD.

Many SRD can be diagnosed by precise and complete history taking. In present illness, it is important to get the information about manner of disease onset, the state immediately before the onset, time course, accompanying symptoms, and response to antibiotics or glucocorticoid in case of recent administration of these drugs. In past history, histories of drug administration, infection, operation, and various related diseases are important. Since some SRD have genetic predisposition, familial history about autoimmune diseases should be investigated.

Physical examination should be done thoroughly, not only in regions of patients' complaints but also through whole body from head to toes. The majority of SRD can be diagnosed by complete history taking and physical examination.

Laboratory tests and other diagnostic procedures are employed to confirm clinical diagnosis. Among them, some autoantibodies are specific for individual SRD and can serve as diagnostic tools. These include antibodies for nuclear components such as double-stranded DNA and Sm, for cytoplasmic components such as myeloperoxidase and proteinase 3, and for citrullinated peptides. HLA typing gives good information in some SRD. Imaging studies are also useful in evaluating organ lesions. Pathological examination of biopsy specimen is crucial for final diagnosis and useful in determining therapeutic regimen.

In this lecture, the above mentioned strategies will be reviewed from the viewpoint of differential diagnosis of SRD.

ACL-2

Basic research on the pathogenesis of rheumatoid arthritis Hiroshi Takayanagi

Department of Cell Signaling Tokyo Medical and Dental University / JST, ERATO

The method to prevent bone destruction in rheumatoid arthritis has never been established to the full satisfaction. This is partly because virtually all the antirheumatic drugs were developed based on their effects on immune reactions. Thus, even in the age of biologics, it is crucially important to understand the mechanism underlying bone destruction, which will surely benefit the development of future therapeutic strategies. How does abnormality of the immune system induce skeletal damage in autoimmune disease? Although the infiltration of CD4⁺ T cells in the rheumatoid arthritis (RA) synovium is a pathogenetic hallmark and is undoubtedly linked to the bone destruction, it has been unclear what type of and how T cells induce bone-resorbing cells, osteoclasts. IL-17-producing T helper cells (T_H17 cells) have been identified to be the exclusive T cell subset that has the ability to induce osteoclastogenesis. IL-17 induces RANKL, the key cytokine for osteoclastogenesis, on synovial fibroblasts and also stimulates local inflammation leading to overproduction of inflammatory cytokines such as TNF-a, IL-1 and IL-6. These cytokines further enhance RANKL expression on the synovial fibroblasts and activate the osteoclastogenic signals in the osteoclast precursor cells by promoting the sensitivity to RANKL. It has been also shown that the development of Th17 depends on IL-6, TGF-b and IL-23. These mechanisms provide a molecular basis for novel therapeutic strategies including the antibodies against RANKL, IL-6, IL-23 and IL-17. Recent finding on the transcriptional regulation of Th17 development will also be discussed.

ACL-3

Juvenile Idiopathic Arthritis: Clinical Approach

Shumpei Yokota

Yokohama City University School of Medicine, Department of Pediatrics

Most part of chronic arthritis in childhood is juvenile idiopathic arthritis (JIA). Recent development of biologic response modifiers or biologics is attributed to the concept shift of the diagnosis and treatment of JIA. The earlier the diagnosis is, the better the prognosis will be expected. The accurate diagnosis approach includes an early detection of joint inflammation, an estimation of magnitude of inflammation, and a presumption of prognosis. It is an important issue to start the standard treatment regimen in order to choose the children who are not responded well to the first line treatment. Those who are unresponsive to the treatment will be the group for biologics. Clinically, the children affected with arthritis are firstly interviewed when the joint pain starts in the morning and whether the both sides of joints are affected, and then received physical examination on each joint around 70 sites. The ultrasound examination will be helpful to detect active joint inflammation. Then, the classification of JIA should be reminded according to the WHO/ILAR criteria. The blood examination includes CRP and ESR as the inflammatory markers, rheumatoid factor, anti-nuclear antibody and anti-CCP antibody for the estimation of prognosis, and MMP-3 as the cartilage destruction marker. The treatment schedule will be the next matter to be considered. The world-wide standard for the first line treatment regimen is the weekly methotrexate (MTX, 10 mg/kg) (+ prednisolone 5-10 mg/day). Rehabilitation for the joints unaffected and the ophthalmological examination are recommended. Two to 4 weeks after the initiation of the therapy, the efficacy of MTX can be estimated by physical and ultrasound examination on the next visit. In case a patient with polyarticular JIA still has active arthritis after 3 months treatment, the application of biologics will be considered; polyarticular JIA patients with positive anti-CCP antibody are those who would be applied the biologics much earlier. Children are the people on developing and maturing, and the restricted movement by joint pain and swelling will deeply hurt them and strongly affect on their life. Thus, rheumatologists should be careful in choosing the appropriate treatment for JIA patients with prospect in the future.

ACL-4

Diagnosis of Rheumatoid Arthritis by 2010ACR/EULAR Criteria and Imaging Diagnosis

Akira Sagawa

Sagawa Akira Rheumatology Clinic, Sapporo, Japan

Recently Rheumatoid Arthritis (RA) has now been considered to be one of the curable diseases, if the treatment started in early disease period.

This phenomenon owes to progress of new and effective treatment representing biologic agents such as TNF- α inhibitor, IL-6 receptor inhibitor and T cell modulator.

Therefore we should find new RA patients and diagnose correctly as early as possible, then start proper treatment for the patients diagnosed as RA.

In these circumstances, newly proposed RA Classification Criteria of 2010ACR/EULAR is now very useful for screening and diagnosing early RA patients from others. This criteria comprises from four items such as 1.Number of Joints with Synovitis, 2.Seropositivity, 3.Duration of disease, 4.ESR, CRP.

Among these items, most important and fundamental item is the presence of synovitis for screening RA. In order to find and diagnose synovitis, imaging tools such as MRI and ultrasonography has now been shown very effective besides physical examination.

Today's topic is the diagnosis of early RA by 2010ACR/EULAR criteria using imaging method.

ACL-5 Drug therapy for rheumatoid arthritis

Hideto Kameda

School of Medicine, Keio University

The therapeutic goal of rheumatoid arthritis (RA) is to prevent organ damage, especially joint destruction, the decrease in the activity of daily life, and the lifetime shortening. Therefore, we need to regard "disease activity" as the time-differentiated organ damage, and consequently, properly evaluate and control the activity and severity of RA. Clinical remission should be the state in which RA patients should not experience any disability for a long time. Although it is a realistic goal of RA treatment, a less stringent control may be an alternative for some patients with co-morbidities and pre-existing organ damages. Nowadays methotrexate (MTX) is the anchor drug for RA. However, other disease-modifying anti-rheumatic drugs (DMARDs) than MTX are suitable for some patients with co-morbidities, pregnancy wish, or little activity and severity. Accumulating recent evidences indicate that the efficacy of MTX as well as anti-cytokine biological agents largely depends on whether a sufficient dose of those agents are given for each patient or disease. Patients who are unable to receive MTX at all, or sufficiently, due to co-morbidities, in turn, tends to remain high-risk without enough efficacy of anti-TNF biologics and consequent prevention of organ damage. Thus, further alternative therapeutic agents are needed for those patients. In terms of cost-risk-benefit balance of view, remission induction and maintenance therapy should be separately considered. Biological agents, as well as the inhibitors of JAK and Syk, may be best applied for remission induction. By contrast, conventional DMARDs including MTX are suitable for a long-term use in the maintenance phase. In this context, we are performing BuSHIDO trial, in which the addition of bucillamine to MTX has been examined for the efficacy on the decrease in the flare rate after the successful discontinuation of infliximab.

ACL-6

Treatment of rheumatic disease covered by health insuarance:From themedical economic perspective

Nobumasa Miyake

Miyake orthopedic clinic, Shizuoka, Japan

The introduction of biological products (hereinafter "Bios") has given a whole new look to RA outpatient treatment. On the other hand, these drugs are not being prescribed to patients as much as they should. The major reason for this is not so much the patients' concern for adverse reactions but the drug's high prices. Bios cost a total of approximately 100 billion in Japan, and, because of this, medical service fee is estimated to have reached 390 billion. A burden that a disease places on a country is called a Burden of Disease (hereinafter "BD"). BD is expressed in terms of calculation of costs. BD's direct costs include health insurance costs which are direct medical fees, and fees for alternative treatment used other than drugs. Direct non-medical fees include costs for nursing care, home remodeling, and self-help devices, etc. BD's indirect costs refer to labor losses. In other words, they are losses from fees required for going to a hospital, discontinuation of work due to worsening of a medical condition and retirement from work.

Indirect costs are generally said to be approximately twice as much as direct costs. A doctor's most important role is to reduce these labor losses even at the expense of medical costs.

The best time to start Bios therapy is an early stage of RA. Becoming Bio-free will contribute the most to reducing BD. And second best time to start Bios therapy is the stage before impairment of leg joint. It is the biggest factor that raises indirect costs or labor losses. Moreover, the ideal time to start using Bios should differ, depending on individual patient's lifestyles.

Based on EBM, the inherent role of a physician is to choose the best treatment at a particular juncture. You are encouraged to carry out clinical practice while keeping in mind the alleviation of the burdens placed on our country as well as on the patients.

ACL-7

Recent Surgical Treatment for Rheumatoid Arthritis Hisaaki Miyahara

Dept. of Orthopaedic Surgery, and Rheumatology, Kyushu Medical Center, Fukuoka, Japan

Remission is realistic goal of current early aggressive therapy with MTX and biologics for rheumatoid arthritis (RA). Not only clinical remission, but functional remission must be reached. By the recent use of biologic agents, severity of the disease is decreasing. However, non-responders to medications and the patients who cannot use them due to comorbidities still exist. The use of biologic agents inhibits progression of joint destruction, but joints with higher grade of destruction at baseline show gradual deterioration. Therefore, surgical intervention is needed to get complete functional improvement or remission. Recent surgical treatment for rheumatoid arthritis, operative indications, timing and procedures are discussed in this lecture.

Synovectomy: The improved control of the inflammatory process by new drugs such as biologic agents has lead to a decrease of acute painful synovitis and therefore to a decrease of synovectomies. Early stage synovectomy is now rarely performed except for a few joints with residual synovitis for which medication is not effective.

Arthroplasty: Sauve-Kapandji's operation is recommended as stabilizing procedure for the unstable wrist. Resection arthroplasty is applied to the forefoot deformity.

Arthrodesis: Arthrodesis produces stability. It is indicated for the unstable wrist, thumb IP joint, ankle, and other joints.

Total joint arthroplasty: The pain relief after total shoulder arthroplasty (TSA) is excellent, but the better result are obtained when rotator cuff is preserved at the time of operation. Total elbow arthroplasty (TEA) is a well-established procedure for the RA elbows with intractable pain or limited motion. Total hip arthroplasty (THA) and total knee arthroplasty (TKA) achieves early functional recovery of the patient and has long term durability. The delay of the timing of the operation becomes the cause of the contracture, muscular atrophy, and the bone atrophy and poor functional outcome as a result.