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EDITORIAL

Window of Opportunity in inflammatory rheumatic diseases

Mohammad Bagher Owlia[1]

[1]*Department of Internal Medicine, Shahid Sadoughi Hospital, Shahid Sadoughi University of Medical Science, Yazd, Iran.*

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Rheumatology is a rather young science with a huge issues to be elucidated in future. In early rheumatology era, the main concern was to detect acute rheumatic fever to prevent future rheumatic heart disease or treat a gouty or infectious arthritis in a right fashion. After years, a vast majority of different rheumatologic conditions defined and categorized. Rheumatoid arthritis (RA), systemic lupus erythematosus, systemic sclerosis, inflammatory myopathies, seronegative spondylarthritides, vasculitides and some more new categories.[1] For years, cut point of initiation of antimalarial agents in rheumatoid arthritis was observing bone erosions in simple wrist X-ray of patients with long lasted synovitis while at the present time there is a consensus to start effective DMARDs upon diagnosis of synovitis in RA.

According to Collins dictionary **window of opportunity (WO)** is defined as "an opportunity to do something that will only last for a short time and needs to be taken advantage of quickly".

The worst scenario in case of infectious diseases is overwhelming sepsis and irreversible shock and death. The reason is over secretion of toxic mediators of inflammation for un controlled infection that may goes to death within hours.[2] This scenario is true for other non-infectious inflammatory conditions (rheumatologic disorders) with a lower speed in most instances. However catastrophic acute immunologic reactions can also be fatal within hours or days. Anaphylactic reactions and catastrophic APS are good examples for this fact. This is important to remember that few if any of offending microorganisms can breakdown the body without intermediary action of immune system. So "aberrant immune system" can potentially harm human body. In some instances overwhelming immune response may shut down the whole organism within hours while abnormal immune response as occurs in most rheumatic conditions usually harm specific organ (s) in a matter of months or even years. Despite the fact that critical window of opportunity in infectious diseases and only some non-infectious diseases are extremely short, however, this opportunity for rheumatologic conditions are not too long to be postponed due to underestimation of burden of diseases. Albeit endpoint of most rheumatologic disorders are organ failure rather that death in most instances.

Herein we discuss on major rheumatological condition in daily practice.

Correspondence:
Mohammad Bagher Owlia MD, Rheumatologist
Professor of Medicine
Department of Internal Medicine, Shahid Sadoughi Hospital,
Shahid Sadoughi University of Medical Sciences,
Yazd, Iran
E-mail: editor@journalofcasereport.com

RHEUMATOID ARTHRITIS (RA)

For decades RA was considered as a joint disease with occasional extra-articular manifestations. According to new concepts of RA, this condition is a multisystem disease more evidently presented as a joint diseases. As mentioned earlier, Years ago the goal of therapy in RA was to halt progression of pre-existing bone erosion. Some more conservative physicians have been uncertain to start DMARDs before positive laboratory tests in a relevant clinical setting while now we clearly now that RA usually presents with subtle extra-articular (mucosal, pulmonary or vascular) manifestations years before joint show.[3] Sometimes dry eye may be the first clue heralding RA in future.[4] So initiation of preventive and therapeutic measures seems to be mandatory in pertinent settings in very early disease.[5,6]

SYSTEMIC LUPUS ERYTHEMATOSUS (SLE)

Fewer articles are dealing with WO in SLE that could be due to overall consensus regarding unpredictable and potentially wild behavior of SLE among almost all clinicians. Weight of therapeutic burden should critically be assessed before initiation of aggressive therapy. However minimal protective measures such as UV protection, vitamin D supplementation7 (as a major inhibitor of dendritic cells which are the main APC in SLE subjects) and antimalarial agents like HCQ (that can potentially decrease auto-antigenicity)

could alter the natural course of the disease in a safe manner. Author of this article believes that opposing the un-opposed estrogen activity with progestins could be a physiologic strategy against SLE. Progesterone could be a good candidate and third pod of stable preventive measures in subclinical female SLE patients.[7] Little studies are addressing to this important issue of hormonal imbalance as a predisposing factor in SLE and we believe that this unappreciated issue could be an interesting subject in future studies.

SYSTEMIC SCLEROSIS (SSC)

Although evennew therapeutic measures could not effectively prevent progression of SSc in most instance, however addressing important initial features of SSc is very important. Raynaud's phenomenon, puffy hands, early fibrotic lung changes and early phases of skin stiffness are among the emerging clinical features of SSc. In early diagnosis of SSc, one should consider scleroderma-like phenomena as well.

ANKYLOSING SPONDYLITIS (AS)

Inflammatory axial pain is the initial important feature in AS. Underestimating significance of this non-specific early feature along with local considerations of most so-called soft tissue rheumatic diseases such as plantar fasciitis (calcaneal spur8, coccygeal pain9, xyphodynia or intercostal enthesitis-induced chest wall pain), poor understanding of clinical spectrum of huge range of connective tissue diseases[10] and superstitious overestimations of mechanical back pain in young men are the main reasons for the potentially longest delay (about 8 years) in establishing the diagnosis of AS among all specific rheumatologic conditions.[11] under-appreciation of sacroiliac joints in routine clinical practice and imaging requests are another acting factors.[12] Fortunately early referral to rheumatologist by young practitioners resulted in sooner diagnosis in recent years.[13] It seems that early clues in favor of limitation of chest expansion and/ or vertebral flexibility is the critical point in early WO in AS and warrants early initiation of effective therapy. MRI studies may disclose very early changes in spinal endplates and sacroiliac joints only after understanding a broader definitions for spinal inflammatory conditions and proper treatment.[14]

VASCULITIS

Most of vasculitides are clinical entities upon initiation of pathology, however, early manifestations of most necrotizing vasculitides are rather non-specific and subject to overlooking. Fever, malaise and anorexia are among these constitutional symptoms in these settings. Isolated cutaneous vasculitis are usually the sole vasculitis of minimal significance and self-limited in most instances. But other vasculitides are usually life or organ threatening and early diagnosis and prompt medical intervention is crucial. ANCA associated vasculitides (GPA, EGPA, MPA) are generally present with pulmonary, renal, skin or neurologic manifestations with evidence of extravasation of RBCs from the capillary bed. Diffuse alveolar hemorrhage (DAH) is the most devastating vasculitic condition with rapidly progressive course and universally fatal if left untreated. In recent era, DAH is better diagnosed and managed with better outcomes. Upon making diagnosis of DAH, intensive immunosuppression and possibly plasma exchange is standard of care that dramatically improved disease outcome. DAH could be the single vasculitic condition that needs emergent medical intervention even before establishing the primary cause of it due to its grave behavior and very high chance of emerging death.

Giant cell arteritis (GCA) is the tricky one with more indolent course that can be ignored for months or even years. Initial non-specific manifestations are usually followed by a quiescent clinical but not pathological phase. So attention should be made in potential cases of Takayasu arteritis or temporal arteritis.

For years the main clue to diagnosis of TAK was absence of radial pulses along with persistently elevated ESR and possible other signs of inflammation within the body. This approach no longer could be a rational one due to long delay in detecting and preventing the progression of pathology. We suggest any cryptogenic fever or other constitutional features with persistently elevated ESR in pertinent clinical setting should be "actively" screened for possible TAK in "pre-pulseless" period. Due to inherent tendency to major vessels, we would suggest any sensitive imaging technique such as MR angiography or even PET-CT scan to detect early nidus for vessel wall inflammation.

IDIOPATHIC INFLAMMATORY MYOPATHIES (IIM)

Unique feature of IIM is subtle initial features that can be easily overlooked. Prodromal symptoms such as constitutional symptoms are usually non-specific and similar to other connective tissue disorders. Early muscular features are usually not the patients' complaint and only can be diagnosed with comprehensive physical examination. Pain may be accompanying complaint in about half of patients and can be easily misdiagnosed as other common painful rheumatologic conditions other than myositis. Muscle weakness on the other side is a tricky condition that could be subject to underestimation especially in initial phase even with standard physical examination on bed. In most cases inability to stand upon sitting and resist against an external force in upper limbs are the most valuable physical findings.

Laboratory investigations addressing to IIM are also not as routine as other laboratory tests. Up to 50% of patients with IIM may have normal muscle enzyme levels in some course of disease and serum aldolase could be a clue for diagnosis.

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