

EDITORIAL

History, concept and spectrum of rheumatism, challenges in understanding

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Joint diseases are among the most documented medical facts through the history; from the time that remnants of destructed joints from bodies were discovered in the lands of early civilizations like Nile or Indus River valley.

History of rheumatism goes back to hundreds of years before Christ. When Hippocrates discussed about gout (general term used for a destructive joint disease according to modern terminology) in men and women and eunuchs.¹

First descriptions of rheumatism were denoting to “joint” illnesses. This is important, because for years we know that rheumatic disorders may affect near all organs in the body and rheumatology is actually a “ubiquitous science” that could not be defined as the science of “joints” only, and is not limited to joints. However, after thousands of years, the term “rheumatism” still brings in mind initially and mostly a chronic “joint” problem. From historical point of view, rheumatism first used to describe the clinical pictures of acute joint inflammation secondary to acute rheumatic fever (ARF) and hyper-acute joint inflammation or chronic poly-articular deforming knobby joint disease suggestive of acute and chronic tophaceous gout. This was the reason that even most today’s physicians unreasonably ascribe acute joint inflammation to ARF and we observe over-diagnoses of this rare condition.² That times, the other joint disease covering the term rheumatism was deforming osteoarthritis.

For years, syphilis was the culprit condition for many joint problems, probably due to its serologic cross-reactivity with some autoimmune disorders.³ So etiopathophysiology was a less important issue in nomenclature of “rheumatism” in the past.

Avicenna (Ibn-e Sina), the great Persian polymath (980 -1036), believed that humidity and cold temperament make people susceptible to joint problems and rheumatism.⁴ In 13th century, all joint ailments were named “gutta” as a general term, then the specific term “gout” was used instead.

In 1642, Ballonius used term “rheumatism” to distinguish true rheumatic diseases (noxious humors)

from catarrh (atopic diatheses). So he (and possibly Avicenna) had been understood the possible common underlying mechanism, i.e. involvement of immune system in these two categories.⁵

Thomas Sydenham (1676) clearly discriminated acute arthritis from chronic destructive joint disease.⁶ In 1695, the term “ankylosing spondylitis” (AS) was used for the first time by Royal Society of London. After a while, the term “rheumatoid arthritis” was used by Garrod (1890) to describe a disease resembling (-oid) “true rheumatism”, i.e. rheumatic fever.⁷

Conceptualism of rheumatism developed through the history from an anatomic issue (joints) to histologic pathology potentially in any organ (carditis, autoimmune pancreatitis) and now to ubiquitous molecular entity (cytokines and clinical immunology) during a couple of decades.

Modern classification of rheumatic disorders was established around 60 years ago. For better understanding of concept of rheumatism, let us classify major categories of diseases according to authors’ understanding.

If we look at the present illnesses, we actually can classify them to the main following categories: Congenital anomalies, defined genetic disorders, developmental, degenerative (aging), psychological, infectious, traumatic, and immune-mediated (rheumatic) diseases, benign infiltrative disorders such as accumulation of abnormal proteins (amyloidosis) or elements (Wilson’s disease), and finally (malign) neoplastic diseases.

There are notable overlapping in some occasions. For example several congenital disorders are associated with inflammatory conditions or many immune-mediated conditions evolve to frank neoplasm over years. Familial Mediterranean Fever (FMF) could be a model of inter-tangled genetic and rheumatic condition. Considering the above facts and as a general speaking, almost any painful, inflammatory, edematous/ tumefactive condition of any organ could potentially be categorized as a rheumatic disease after ruling out of other mentioned and/ or non-mentioned specific causes. This is especially true when a dramatic and sustained response to anti-inflammatory agents is notable. Because the least specific and multivariate concept among them is rheumatism. Cell infiltration

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in inflammatory and rheumatic conditions is not unique and all inflammatory cells can potentially play a role: polymorphonuclear cells (periodic syndrome, auto-inflammatory diseases), lymphocytes (most classic rheumatic diseases), plasma cells, macrophages, platelets⁸ or eosinophils (eosinophilic synovitis). So, infiltration or activations of immune cells *de novo* or via cytokines are considered as the least determinant issue in rheumatism as a general term.

Recently has been shown that any insulting agent that could hurt tissues may lead to local or even systemic inflammatory diseases via specific molecules “alarmins” (danger signals) mostly derived from mitochondria.⁹

Definition of inflammation (tissue response to injury) as a cornerstone of rheumatism only covers some spectrum of whole concept of rheumatic diseases, because we pretty know that some well-known autoimmune disorders lack overt inflammation (anti-phospholipid syndrome or IgG-4 related systemic disease, pauci-immune glomerulonephritis) but rheumatism still exists. The key feature in near all rheumatic conditions is an “ongoing benign pathology” with defective “switch-off” mechanisms as normally seen in other non-rheumatic inflammations such as trauma or most offending infections.

To be encountered with rheumatism, we only need to have one of these features: inflammation, cell infiltration or systemic immune response in the absence of obvious inciting and detectable infectious, traumatic or neoplastic factors. This gets to be more sophisticated when such soft tissue or non-articular rheumatism as fibromyalgia, which was commonly believed to be a psychosomatic disorder and systemic inflammation is unlikely to occur, clues to systemic inflammation are shown to be present.¹⁰

From the clinical point of view, widespread use of non-steroidal and steroidal anti-inflammatory drugs and good response to them in almost all painful or inflammatory conditions could indicate the ubiquity of inflammatory conditions in clinical practice. Another evidence supporting the role of inflammation in pathophysiology of diverse conditions, is the pivotal therapeutic role of adenosine as a potent anti-inflammatory agent in supra-ventricular arrhythmias and even rheumatoid arthritis.^{11,12}

A skim review on most anti-neoplastic drugs also discloses that the basic pharmacology could be similar to anti-rheumatic drugs. We actually believe that immune aberrancy (the pivotal point in rheumatic and neoplastic diseases) could be as little as allergic rhinitis, to more sophisticated and chronic as many classic rheumatic conditions or more organ-destroying as seen in a frank neoplasm.

If isolated CNS vasculitis, single organ vasculitis, or antiphospholipid antibody syndrome (for example recurrent abortions) are some topics of vascular rheumatology, so several other conditions such as

multiple sclerosis (CNS rheumatism), Guillain-Barre syndrome, autoimmune inner ear disease, sudden sensorineural hearing loss (ear rheumatism), isolated uveitis, scleritis, allergic chronic sinusitis, most kinds of thyroid dysfunctions, diabetes mellitus (endocrine rheumatism destroying beta cells), bronchial asthma, pernicious anemia, vitiligo, inflammatory bowel diseases (intestinal rheumatism), isolated idiopathic chronic pericarditis, several kinds of auto-inflammatory bone disorders including chronic recurrent multifocal osteomyelitis (CRMO)¹³, non-specific kinds of osteitis (condensans ilii)¹⁴ could be considered as out layers of broad concept of rheumatism. Similarly, idiopathic thrombocytopenic purpura (ITP) could be the first manifestation of frank systemic lupus erythematosus years before the diagnosis.¹⁵ However, it does not mean absolutely that all mentioned conditions should directly be managed by a rheumatologist.

Detection of a batteries of immunological markers in the above conditions support this hypothesis. Interestingly, positive results of autoimmune tests and antibodies such as antinuclear antibodies (ANAs in case of Hashimoto's thyroiditis or ulcerative colitis) are usually interpreted as “false positive” laboratory findings! The similar story could be true for getting positive test results for rheumatoid factor in elderly patients with so-called (but possibly as a true rheumatism) erosive osteoarthritis. Recently, with advances in detection of autoantibodies, for example anti-cyclic citrullinated peptide (ACPA), many cases of so-called erosive or generalized osteoarthritis now are categorized as RA based on new EULAR/ACR 2010 classification criteria for rheumatoid arthritis (RA). Before this (and even at present time!) a tremendous amount of patients with RA were innocent victims of misdiagnosis as osteoarthritis.

Role of immune-mediated organ damage in thyroid gland and pancreas, leading to hypothyroidism and/or diabetes mellitus, is basically similar to that occurs in joint destruction in case of severe untreated rheumatoid arthritis. But in fact, focusing on supplemental treatment (thyroid hormone and insulin replacement) in cases of hypothyroidism and diabetes mellitus has been replaced with primary prevention of immune invasion as it occurs and leads to joint damage in RA. We could conceptualize that early detection and inhibition of immune invasion to thyroid and pancreas may potentially prevent permanent endocrine dysfunction leading to hypothyroidism or diabetes mellitus.

Role of classic educational materials in misunderstanding the concept of rheumatism should not be under-emphasized. Among them “classification criteria” are possible culprit factors for misconception of whole rheumatism for undergraduates. In practice, most clinicians could not count on undifferentiated connective tissue diseases and consider them as an “incomplete” or “immature” rheumatism not as a “true” one. So that, many practitioners fear treating

undifferentiated diseases because it may cause them to be charged as a clinical malpractice. However, most intellectual rheumatologists know that classification criteria are not designed for individual clinical purposes and are mainly proposed for research and epidemiological applications. So, judicious and adjusted treatment is prudent in any phase or any part of the spectrum of immune-mediated diseases.

Taken together, providing a comprehensive and ideal description for concept of “rheumatism” seems to be a difficult task and remains to be proposed.

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