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The WCC Note™

Presented by Stephen J. Pomeranz, M.D.

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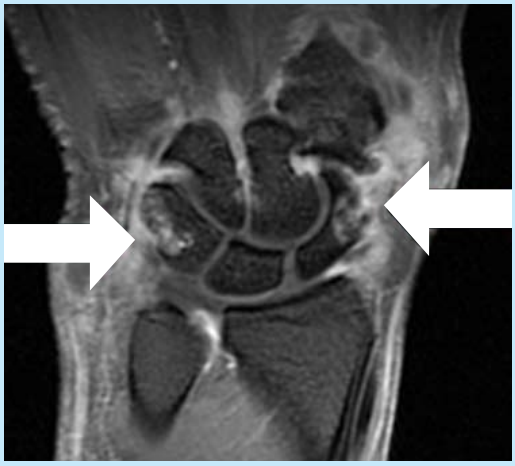
JOINT PATHOLOGY

Rheumatoid Arthritis: How MRI Changes Our Understanding

Rheumatoid arthritis (RA) afflicts 1.3 million Americans. (1) A systemic disease, it affects the joints, skin, blood vessels, heart, lungs, and muscles. While most prevalent between ages 40 to 70, it occurs at all ages, afflicting women two to three times more than men. (2) The ability of MRI to depict soft tissue and bone marrow has widened our perception of the disease and made MRI a modality of choice for RA diagnosis, assessment and, subsequently, clinical trial evaluation.

The joint pathology occurs in stages:

1. Synovium swells and becomes hyperplastic.
2. Inflammatory cells infiltrate synovium.
3. Vascularity increases from vasodilatation and angiogenesis.
4. Organized fibrin covers some synovium and releases into the joint as rice bodies.
5. Osteoclastic activity occurs in subjacent bone, with erosions, cysts, and osteoporosis developing.
6. Masses of synovium, inflammatory cells, granulation, and fibroblasts, called pannus, occur.
7. Inflamed cells release enzymes that destroy cartilage and bone. (2)



Wrist MRI showing rheumatoid arthritis (arrows).

This issue of ***The WCC Note*** continues our series outlining some of the recent literature on RA. This week's articles address searches to elucidate the etiology of rheumatoid arthritis, since understanding its pathogenesis is requisite to optimally preventing or arresting joint destruction. ■

PATHOGENESIS FACTORS

The Components of Pathogenesis

General theory holds RA to be an autoimmune disease incited by an arthritogenic antigen in a genetically susceptible person. Each of these factors – genetic susceptibility, antigen, and autoimmune reaction – plays a role.

1. Genetic susceptibility

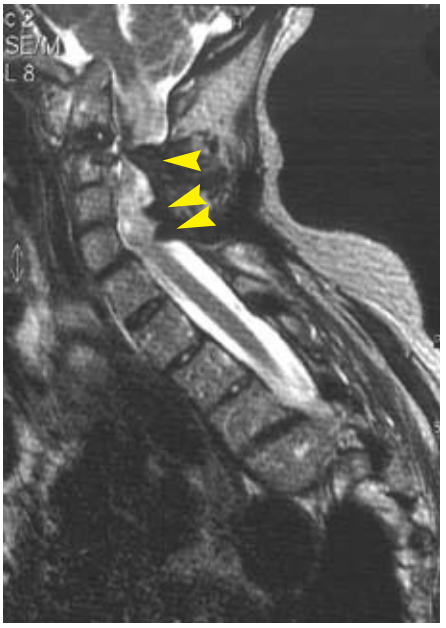
a. Genetic factors predispose to RA, though their overall contribution is estimated at 50 percent or less. Other nongenetic but gene-regulating factors may influence a person's susceptibility to RA and disease severity. Called epigenetic factors, these are heritable alterations in gene expression without changes in nucleotide sequence – in other words,

alterations in gene expression without changes in nucleotide sequence – in other words, changes not encoded directly by DNA sequence of the specific gene, but instead such entities as DNA methylation or noncoding RNAs. Strietholt, *et al.*, reviewed such epigenetic processes in RA. The authors note that epigenetic modifications, while not fixed in DNA code, can be stable during a person's life or can be altered by individual lifestyle differences. Environmental triggers are hypothesized to participate in the RA by causing epigenetic modifications, which are thought to play a major role in RA's development. (3)

2. Autoimmune reaction

a. Reviewing what MRI has told us about the pathogenesis of RA, McGonagle and Tan report that MRI-demonstrated synovitis shows high correlation to histological grades of synovitis and tissue vascularity, and appears to confirm RA as primarily a disease of synovium. They state their studies show erosions occur secondarily due to synovitis, with sites of joint compression possibly more prone to erosion, and that effective treatment of synovitis is crucial to successful therapy. (4)

b. To determine the cellular components of MRI bone edema in RA, Dalbeth, *et al.*, examined 11 patients with RA who were undergoing orthopedic surgery. They found an increased number of osteoclasts, RANKL (**R**eceptor **A**ctivator for **N**uclear factor **K**appaB **L**igand), macrophages, and plasma cells in samples with MRI bone edema, concluding that RA bone erosions result from activation of local bone resorption of subchondral bone as well as synovial invasion. (5)



Cervical spine MRI of patient with rheumatiod arthitis with stenosis (arrows).

c. Histopathological studies depict lymphocytes and osteoclasts in subchondral bone that could mediate erosions from the marrow toward the joint, according to a report from the Department of Molecular Medicine and Pathology at the University of Auckland, New Zealand. The authors state that animal models show evidence that this cellular infiltrate corresponds to MRI bone edema, supporting the notion that bone-marrow pathology helps drive joint damage. (6)

d. Macrophages of RA patients possess signaling pathways that drive continued production of pro-inflammatory mediators in effected joints. Noting that current pharmaceuticals are biological agents blocking a cytokine (tumor necrosis factor) produced predominantly from macrophages, authors from Imperial College of Science, Technology and Medicine in London, U.K., discuss the various signaling mechanisms in innate immune cells. (7)

***Conclusion:* Several recent studies advance our understanding of the origin of rheumatoid arthritis, theorized to be an autoimmune disease triggered in a genetically susceptible person by an inciting antigen. Areas under continued scrutiny include patient epigenetic factors, the dominant role of synovitis, and evolving evidence that bone-marrow pathology participates in joint damage. Research documents the cornerstone role magnetic resonance imaging has played in furthering our knowledge about the disease. ■**

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Next Issue: A review of studies addressing how MRI aids in the diagnosis and treatment of rheumatoid arthritis.

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- *Contributing Editors:* Margaret D. Phillips, M.D. (newsletter@wcclinical.com) and Stephen J. Pomeranz, M.D. (newsletter@wcclinical.com)
- *Managing Editor:* Rod Willis
- *Graphic Designer:* Tom Anneken
- *Distribution Manager:* Shannon Roeper