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CONFERENCE PROCEEDING

Rheumatoid Arthritis: Beyond the Basics

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INTRODUCTION

Rheumatoid Arthritis (RA) is a chronic autoimmune inflammatory disorder leading to various protean systemic manifestations along with articular damage. Its prevalence is 0.5-1% globally. It is thrice more common in women. The peak age of onset is 40-60 years.

Etiology

Both genetic and environmental factors contribute to the pathogenesis of RA. The common HLA associations are HLA-DR4, HLA-DR1. Smoking, infections and gut microbiome dysbiosis are some of the important environmental contributory factors. It is hypothesized that ostrogen fluctuations may also play a role, thereby explaining the female preponderance.

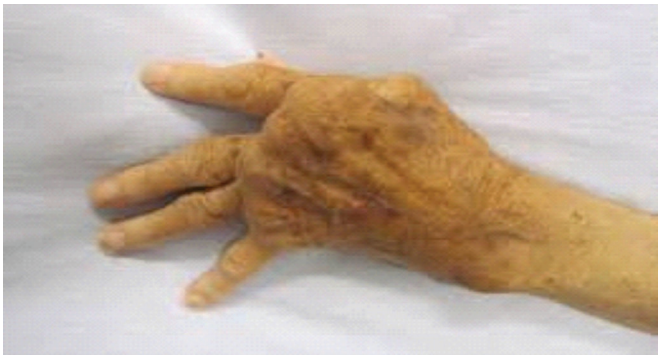

Figure 1: Rheumatoid hand. (Note the ulnar deviation at the metacarpo-phalyngeal joints.)

Pathophysiology

The arthritis is caused by an autoimmune synovial inflammation that involves T-cells, B-cells, macrophages and cytokines (TNF-α, IL-6, IL-1) leading to pannus formation and joint destruction. There is a loss of immunological tolerance that leads to an activation of the adaptive immunity. Th1 and Th17 cells play an important role in the synoial inflammation. The autoantibodies, rheumatoid factor and anti-CCP contribute to the tissue damage

Diagnostic Criteria (ACR/EULAR 2010)

Joint involvement, serology (RF, anti-CCP), acute phase reactants (CRP, ESR) and the duration of symptom are taken into account. A score ≥6 confirms the diagnosis of RA.

Table 1: ACR /EULAR 2010 diagnostic criteria for the diagnosis of RA.

Criteria	Points
Joint Involvement	
1 large joint	0
2-10 large joints	1
1-3 small joints (+/- large joints)	3
>10 joints (at least 1 small joint)	5
Serology	
Negative	0
Low positive RF or anti-CCP	2
High positive RF or anti-CCP	3
Acute Phase Reactants	
Normal CRP and ESR	0
Abnormal CRP or ESR	1
Duration of Symptoms	
> 6-weeks	0
< 6-weeks	1

Imaging Modalities

X-ray, MRI and ultrasound can all be helpful in making the diagnosis of RA. While X-ray findings appear later in the course of the disease, both ultrasound and MRI can help in diagnosing the disease early. The characteristic findings are given below.

- X-ray: Joint space narrowing, erosions
- MRI: Early synovitis and bone edema
- Ultrasound: Doppler signals of active inflammation

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Drugs Used in RA

NSAIDS & Corticosteroids

NSAIDs provide symptomatic relief but do not alter disease progression. Corticosteroids are used to treat short-term flares but have long-term risks. They can also be used for bridge therapy during initiation of DMARDs. The latter have the ability to slow or halt the progression of the disease including radiological changes.

Conventional disease modifying drugs

- Methotrexate
- Hydroxychloroquin
- Sulfasalazine
- Leflunomide
- Azathioprine
- Minocycline
- Cyclosporine
- Gold
- Pencillamine

Biologic DMARDs

- Etanercept
- Infliximab
- Anakinra
- Adalimumab
- Abatacept
- Rituximab
- Certolizumab
- Golimumab
- Tocilizuma

Targeted synthetic DMARDS

- JAK inhibitors (tofacitinib, baricitinib, upadacitinib).
- Offer an oral alternative to biologics.
- Predisposition to develop Herpes Zoster

Latest advances

- Iguratimod- NFkB inhibitor

Approach to treatment- Treat to Target

Methotrexate is the mainstay of treatment and in the absence of contraindications, should be started in all patients once the diagnosis has been made. Leflunomide or sulfasalazine should be started instead, when methotrexate is contraindicated. Most patients require at least short-term glucocorticoids at the start of treatment to control the inflammation quickly. Improvement is expected by the end of three months. If remission or low disease activity is not achieved by six-months, a second DMARD should be added or substituted. In the presence of poor prognostic factors like high titres of rheumatoid factor or anti-CCP, early joint damage or failure to respond to two conventional DMARDs, a biologic disease modifying agent or JAK-inhibitor should be preferred over conventional DMARDs. This should be changed once again, if there is no improvement by three months or if remission or low disease activity is not achieved by six months. At any stage dose reduction (or increase in the interval of biologic DMARD) may be considered if remission has been maintained for more than six months.

Lifestyle and rehabilitation

Patients should be encouraged to undertake low-impact activities that help to maintain joint mobility. Gentle hand exercises comprising (1) opening and closing the hand to maintain a fist, (2) touching each finger one by one to the thumb, (3) stretching the fingers apart and closing them back and (4) flexing the fingers to touch the top of the palm by fingertips can help to preserve function.

Nutrition is important. Patients should be advised to take a balanced diet. Mediterranean diet with omega-3 fatty acids is helpful in maintaining good health. Yoga and mindfulness can help fight stress.

SPECIAL SCENARIOS

Cardiovascular risk in RA

There is increased risk of heart disease in patients in RA. This is associated with increased inflammatory markers, including CRP, ESR, RAF, Anti-CCP2. Lipid profile in RA is characterized by suppression of total and LDL cholesterol, and decreased HDL levels, yielding an unfavourable ratio of total to HDL cholesterol. Carotid Artery Intima Media Thickness is an indirect marker of increased cardiovascular risk.

Cardiovascula risk should be borne in mind when prescribing in a patient with RA. Methotrexate, the first line treatment in RA is associated with lower cardiovascular risk. It does not alter lipid profiles. Hydroxychloroquine is associated with decreased risk of diabetes in RA, and also improve lipid profile. JAK inhibitors may need to be avoided due to their adverse impat on the lipid profile. TNF alpha inhibitors in RA appear to be associated with reduced risk of all cardiovascular events. Overall, biologics in RA may improve the lipid profile but could also have adverse effects on cardiovascular health, hence needs careful consideration. Statins may be given in patients of RA with heart disease. Some studies have found increased risk of myocardial infarction in patients who discontinued statins for over 3-months

PULMONARY MANIFESTATIONS

Interstitial lung disease (ILD) common in RA. HRCT Thorax in prone position can detect early ILD before symptoms manifest. The most common forms of ILD associated with RA are Usual Interstitial Pneumonia (UIP) and Non-specific Interstitial Pneumonia (NSIP). Current treatment regimens usually involve corticosteroid therapy with or without a cytotoxic agent, most commonly azathioprine, mycophenolate mofetil (MMF) or cyclophosphamide. Recent retrospective analyses centered on treatment of RA-ILD with MMF and rituximab have shown promising results. NSIP shows better response to therapy and prognosis than a UIP pattern.

Vaccination for influenza and pneumococcal pneumonia is recommended for all patients. Methotrexate use is generally avoided because of well-documented pulmonary toxicity. TNF-alpha inhibitors should be used with caution in these patients following reports of increased rates of lung toxicity with these agents.

Neurological manifestations in RA

Involvement of the cervical spine is common. RA can affect the atlantooccipital joint (C1- occiput), the atlantoaxial joint (C1-C2), and the subaxial joints (C3-C7). Rheumatoid synovitis and pannus may compress or invade adjacent structures (including the spinal cord and peripheral nerves), resulting in myelopathy, radiculopathy, and entrapment neuropathies**.**

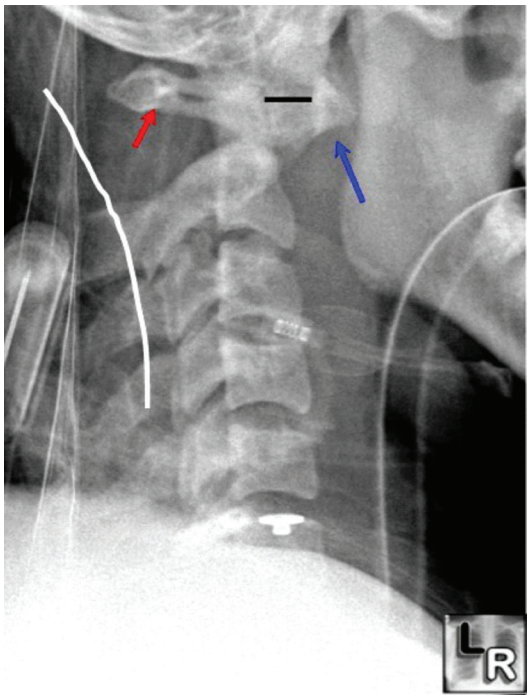

Figure 2: Atlanto-axial sublaxation.

RA in women of reproductive age

RA can cause menstrual symptoms like irregular periods, amenorrhea, and dysmenorrhea. Both RA, and its treatment can impact fertility. Pregnancies should be planned carefully, considering both disease activity as well as the potential teratogenic effects of the medications used.

The physician should try to stabilise the disease activity before conception and switch to pregnancy- compatible medications. These include hydroxychloroquine and sulfasalazine. Prednisolone may be added if needed in the smallest dose required to achieve good control of symptoms. Same drugs should be used during lactation. Folic acid supplementation should be done during pregnancy to prevent birth defects.

Ocular manifestations

The ocular complications of RA include keratoconjunctivitis sicca (dryness and inflammation of the cornea and conjunctiva due to reduced tear production), episcleritis, scleritis and uveitis. These conditions usually present with pain, redness and tenderness of the eye. Uveitis also causes photophobia and blurred vision. Retinal Vasculitis is another condition that leads to blurring of vision and visual loss.

Ttreatment is usually with topical corticosteroids for mild to moderate inflammation. Immunosuppressive medications are needed for more severe inflammation or when corticosteroids are ineffective. Biologics may be needed for refractory cases. Ophthalmology consultation must be taken in all cases.

RA and the liver

Patients with RA are at increased risk of developing fatty liver disease, autoimmune hepatitis and primary biliary cholangitis. Rheumatoid nodules may be detected in the liver on imaging. However, the commonest hepatic complication in RA is methotrexate induced liver injury in the form of elevated liver enzymes, hepatitis and liver fibrosis. Leflunomide is also hepatotoxic. Alternative drugs should be used in the presence of liver disease. Interleukin VI inhibitor Tocilizumab may result in elevated transaminases during initial administration, and monitoring of liver function is essential.

CONCLUSION

Early diagnosis and aggressive treatment improve the long-term outcome of RA. A patient-centric multidisciplinary approach should be adopted. All patients must be closely monitored for complications of the disease as well as its treatment.