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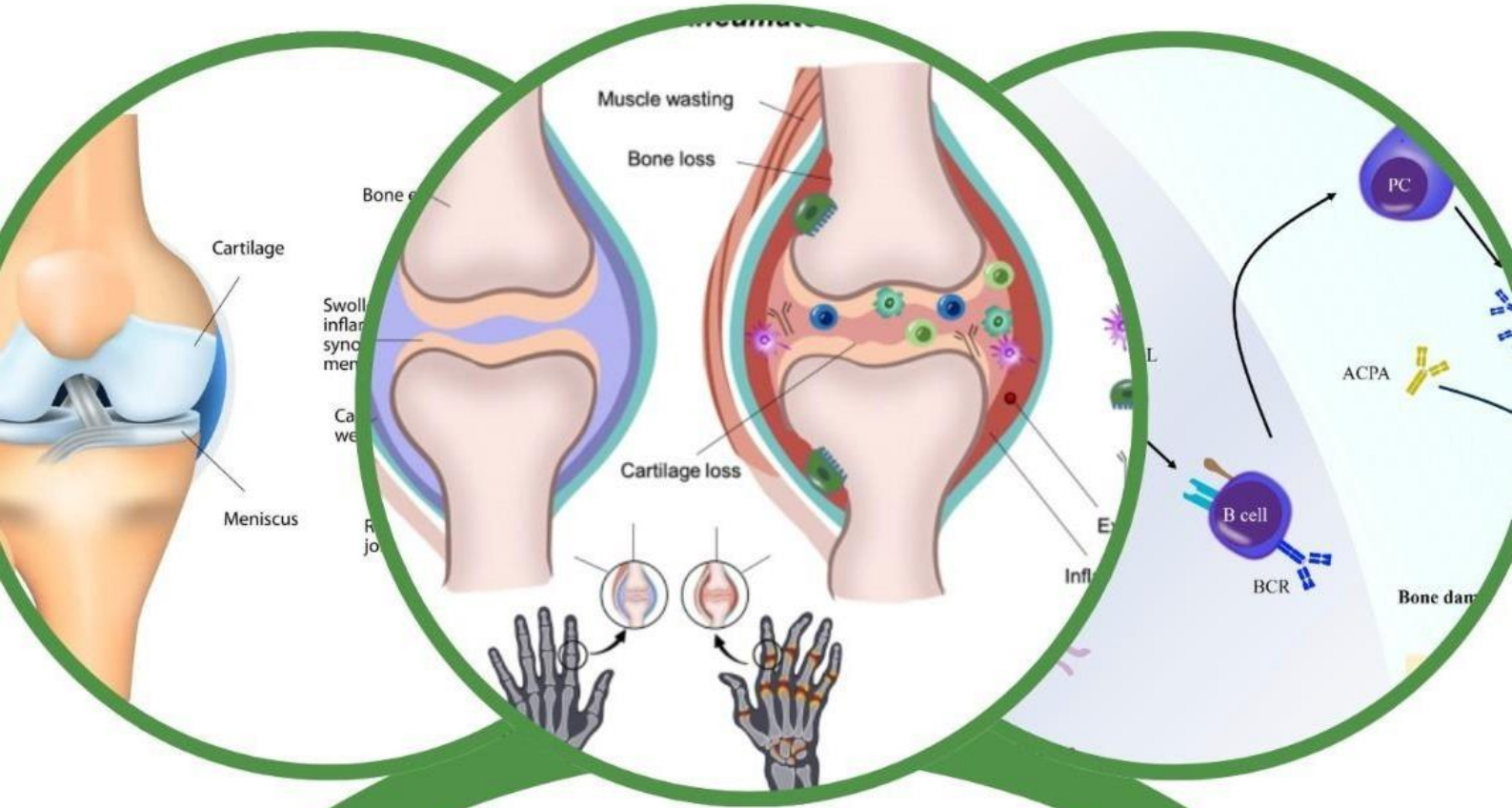

Beyond Joint Destruction :The Underlying Risk of Lymphoma in Rheumatoid Arthritis

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BEYOND JOINT DESTRUCTION: THE UNDERLYING RISK OF LYMPHOMA IN RHEUMATOID ARTHRITIS

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ABSTRACT

Rheumatoid arthritis (RA) is a chronic autoimmune condition characterized by systemic inflammation, predominantly affecting the joints. In contrast, lymphoma is a malignancy of the lymphatic system. Epidemiological research has established a significant correlation between RA and an elevated risk of lymphoma, particularly non-Hodgkin lymphoma (NHL). This association is thought to stem from factors such as chronic immune activation, genetic predisposition, and possible side effects of immunosuppressive therapies. Additionally, the overexpression of p53 mutations, oxidative stress, and dysregulated inflammatory pathways play a substantial role in the development of lymphoma among patients with RA. This review aims to examine the shared molecular mechanisms connecting RA and lymphoma, including genetic susceptibility, immune dysregulation, and epigenetic modifications. It further discusses the implications of RA treatments—specifically methotrexate and biologics—on lymphoma risk. Timely diagnosis and effective disease management are essential for mitigating complications. A comprehensive understanding of these interrelated pathophysiological processes may facilitate the development of targeted therapeutic strategies that enhance patient outcomes and reduce the risk of malignancy in individuals with RA.

Keywords: non-Hodgkin lymphoma, autoimmune disease, chronic inflammation, genetic susceptibility, immune dysregulation, p53 mutations, epigenetic modifications, immunosuppressive therapy, lymphomagenesis, targeted therapy.

1. INTRODUCTION

Rheumatoid arthritis (RA) and lymphoma may appear unrelated at first glance, but their surprising connection presents an intriguing puzzle that continues to engage both clinicians and researchers. RA is an autoimmune long-lasting inflammatory condition marked by progressive damage to joints lined with synovium, along with a variety of extra-articular symptoms that can differ in presentation. RA has the potential to affect multiple joints, with typical signs and symptoms including joint swelling and tenderness upon touch, as well as morning stiffness and limitations in mobility in the affected areas [1], while lymphoma is a cancer that affects the lymphatic system; however, the shared mechanisms that bind these two intricate conditions are both perplexing and significant.

A number of studies examining individuals with diagnosed rheumatoid arthritis have revealed an increased risk of developing malignant lymphomas within this group. Furthermore, there is evidence pointing to a relationship between the severity of RA and the likelihood of lymphoma [2]. Patients with RA display a different incidence of cancer

compared to the general population. This is primarily evidenced by elevated standardized incidence ratios (SIRs; an indicator of risk) that are notably high for lymphoma and lung cancer, while significantly lower for colorectal cancer [3].

The hypothesis suggesting a link between RA and lymphoma is supported by the notion that the disease itself, rather than its treatment, mediates this connection, as chronic RA leads to ongoing immune stimulation and the clonal expansion of lymphocytes [4]. On the other hand, immunosuppressive therapies for RA could impair the immune response's capability to identify and eliminate cancer cells, creating a setting where malignancies are more likely to develop [5]. Previous research has indicated a notable overexpression of the p53 protein in the synovial tissues associated with rheumatoid arthritis (RA).

The p53 tumor suppressor protein plays a crucial role in regulating the cell cycle, repairing DNA, and triggering apoptosis. Mutations in this gene have been associated with the development of various cancerous diseases. It is thought that oxidative damage caused by inflammation contributes to p53 mutations. The increased generation of reactive oxygen and nitrogen species in individuals with RA raises the chance of mutagenic occurrences. Importantly, the p53 mutations found in RA are mostly defined by transition base modifications [6]. Additionally, somatic mutations in the p53 gene have been identified in the RA synovium, as well as in complementary DNA (cDNA) and genomic DNA obtained from cultured fibroblast-like synoviocytes. However, it is important to note that variations in the quantity of these findings have been observed across different studies.

In clinical settings, patients with RA generally exhibit recent occurrences of painful and swollen joints, stiffness in the morning, feelings of general illness, alongside abnormal results in laboratory tests [7]. It is crucial to achieve an early diagnosis and effective monitoring of RA to ensure a favourable outcome. Prompt treatment often leads to a quicker decrease in inflammation, resulting in less structural damage [8]. Ultrasound and MRI have been suggested for both diagnosing and tracking disease activity in individuals with RA [9]. CRP and ESR serve as clinical biomarkers that are commonly utilized to assess the overall inflammatory condition of RA patients [10].

JAK inhibitors represent another widely used treatment for RA, typically administered after the ineffectiveness or intolerance to methotrexate. The JAK/STAT pathway plays a significant role in signalling connected to both cancer and inflammatory processes. Tocilizumab, a monoclonal antibody targeting IL-6R, is approved for the treatment of RA [11].

Rheumatoid arthritis and lymphoma are interconnected through a complex relationship shaped by chronic inflammation, immunological dysregulation, and the impact of disease-modifying therapies. While considerable progress has been made in understanding these interactions, significant gaps persist regarding the precise mechanisms involved and the identification of high-risk patient subsets. This review seeks to consolidate the current body of knowledge, explore potential causal pathways, and assess the implications of various therapeutic strategies. The aim is to establish a foundation for enhanced clinical management and guide future research efforts in this important area.

2. RHEUMATOID ARTHRITIS AND THE INCREASED RISK OF LYMPHOMA

Lymphomas are a diverse set of cancers that arise from the malignant transformation of immune cells mainly found in lymphoid tissues [12]. Lymphomas are conventionally divided into two categories: non-Hodgkin's lymphoma (NHL) and Hodgkin's lymphoma, with NHL accounting for nearly 90% of all cases and Hodgkin's lymphoma constituting the

remaining 10% [13]. NHL can be further classified into T-cell and B-cell neoplasms based on the originating cell type. Emerging research indicates that individuals with rheumatoid arthritis (RA) may exhibit variability in their risk of developing lymphoma.

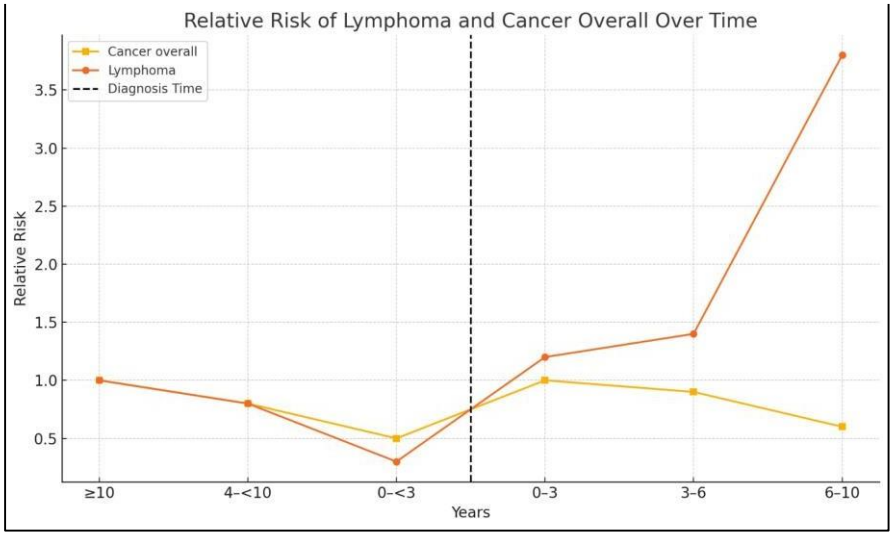

Fig. 1: Relative risk of lymphoma and cancer overall before and after rheumatoid arthritis diagnosis

A notable study conducted in Sweden by Baecklund and colleagues provides compelling evidence linking disease activity to lymphoma incidence among RA patients. This study involved a comparison between 378 RA patients without lymphomas and 378 RA patients diagnosed with lymphomas. Data related to disease characteristics, including the number of swollen and painful joints, erythrocyte sedimentation rate (ESR) values, and the physician's overall assessment score, were collected from medical records starting from the onset of RA until the emergence of lymphoma. The results indicated that RA patients experiencing the highest levels of disease activity were 70 times more likely to develop lymphoma (Fig 1) [14],[15]. Additionally, a smaller cohort study comprising 29 RA patients with lymphoma further substantiated this finding.

3. RISK AND MUTATIONS CAUSED BY MEDICATIONS

The potential link between immunosuppressive medications used in treating inflammatory diseases and increased lymphoma risk has been a topic of considerable debate for years. These medications encompass biologic therapies such as infliximab and etanercept, as well as commonly prescribed disease-modifying antirheumatic drugs (DMARDs) like methotrexate (MTX) and azathioprine. Given the strong correlation between the necessity for antirheumatic treatments and the severity of the disease, it remains challenging to determine whether the development of lymphoma is directly attributable to the underlying disease and its severity or if it is a consequence of the treatments administered [16].

Most larger studies have indicated a minimal risk of lymphoma in patients with rheumatoid arthritis (RA) undergoing long-term methotrexate (MTX) treatment [17]. The significant link between the severity of the disease and the inclination for antirheumatic therapy complicates the understanding of whether disease severity and the underlying pathology contribute to the development of lymphoma or if these factors are actually related

to the treatment. Likewise, an association between azathioprine use and lymphoma has been observed in individuals with autoimmune disorders. However, a meta-analysis by Kandiel *et al*., [18] proposed that the underlying disease and a combination of contributing factors play a more significant role in lymphomagenesis than the impact of azathioprine itself. Additionally, systemic corticosteroids and non-steroidal anti-inflammatory drugs (NSAIDs) are two non-DMARD therapies that may also contribute to lymphomagenesis [19].

4. ROLE OF LIFESTYLE

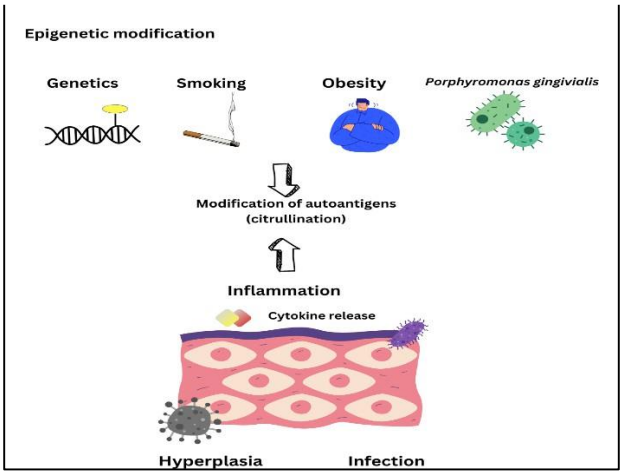

Fig 2: factors affecting RA

The causes of rheumatoid arthritis (RA) are complex, with both genetic and environmental factors playing essential roles in its onset and severity [20]. A well-known risk factor is a genetic susceptibility, as supported by epidemiological research indicating a higher risk among those with a family history of RA (fig:2, [21]]) [22]. Additionally, gender and age significantly affect the condition, with women and middle-aged individuals being more commonly impacted.

Lifestyle factors, such as smoking, high intake of red meat, insufficient physical activity, low consumption of dietary fibers and essential fatty acids, alcohol use, and gluten intake, further increase the risk of RA [23]. Moreover, Dietary fat intake is associated with non-Hodgkin lymphoma (NHL), particularly total, saturated, and animal fats, while the link with monounsaturated fat is weaker. There is limited evidence connecting carbohydrate intake with NHL, but a positive association has been noted for B-cell lymphoma [24]. Various hormonal, dietary, socioeconomic, and ethnic factors also add to the complex nature of RA's development. Notably, many of these factors are interconnected, influencing the disease's course and advancement (Fig 3). It is crucial to comprehend the relationship between genetic and environmental influences to improve the prevention, diagnosis, and treatment of RA [25].

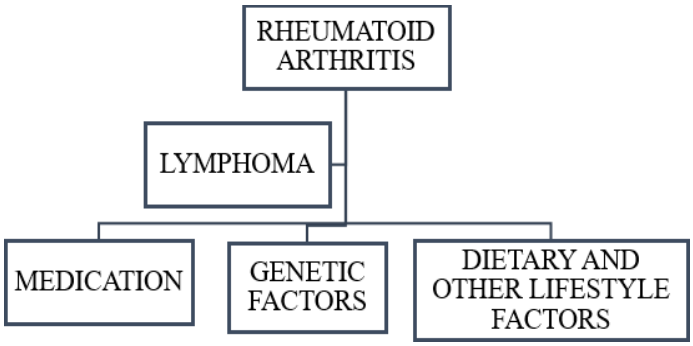

Fig 3: Factors affecting RA and lymphoma

5. GENES INVOLVED IN RA AND LYMPHOMA

5.1. Rheumatoid Arthritis

Genes that are crucial for the development or progression of RA have primarily been identified through the association of variations in genes that encode proteins involved in known immune and inflammatory processes important for joint inflammation [26]. Recent genetic studies have revealed over 150 loci associated with RA, with the strongest associations found with HLA [27]. An early discovery established a genetic link between RA and variations in HLA. As knowledge of the HLA locus architecture has progressed, particularly regarding HLA-DRB1, it has become clear that this link pertains to a group of so-called shared epitope (SE) alleles, particularly pronounced in ACPA-positive RA [28].

Rheumatoid arthritis is an autoimmune disorder marked by immune system abnormalities, including autoantibodies like rheumatoid factor (RF) and anti-citrullinated peptide antibodies (ACPA), measured with anti-CCP ELISA. These antibodies are crucial for RA classification [29];[30].

Recent advancements in the shared epitope hypothesis have revealed independent associations both within and outside the HLA-DRB1 locus [31]. The most significant risk factor identified is associated with valine (Val) at position 11 of the HLA-DRB1 gene, which is characteristic of the HLA-DRB1*04 and HLA-DRB1*10 alleles. Furthermore, other associations have been noted, including lysine (Lys) at position 71 and alanine (Ala) at position 74; however, the connection of these residues to shared epitope alleles remains ambiguous due to their presence in non-shared epitope haplotypes. Glutamic acid (Glu) at position 71 appears to have a protective effect. Additional associations have been recorded with HLA-B, HLA-DPB1, and HLA-A concerning ACPA-positive rheumatoid arthritis, characterized by lower effect sizes for aspartic acid (Asp) at HLA-B position 9; phenylalanine (Phe) at HLA-DPB1 position 9; asparagine (Asn) at HLA-A position 77 [32].

The connection between ACPA-negative rheumatoid arthritis (RA) and the HLA locus presents a less significant risk factor (Han *et al*., 2014). The most notable association was found with the amino acids leucine (Leu) and serine (Ser) at the 11th position of HLA- DRB1, resulting in an odds ratio of 1.22 when compared to healthy subjects. Interestingly, most classical haplotypes containing these amino acids at position 11 of HLA-DRB1 are either associated with HLA-DRB3 or do not correlate with other HLA-DRB genes, such as

HLA-DRB1*01 [33]. This finding underscores that the genetic associations of HLA variants across different RA subtypes and populations are significant contributors to the disease's genetic risk. It is essential to explore non-HLA genetic associations to understand their role in the development of RA.

Various associations outside the HLA locus have been discovered, including genetic variants in the PTPN22, CTLA4, and PADI4 genes. The emergence of cost-effective genotyping techniques and transethnic meta-analyses has broadened this range to include 151 loci across all human chromosomes, except for chromosome Y. Many of these genes are critical for functions specific to the immune system or general cell signaling pathways, indicating that the consequences of these genetic associations with RA may impact various cell types, tissues, and organs beyond the immune system [32].

To discover differentially methylated sites (DMS) particularly related to RA development, genetic association signals for RA were combined with DMS data from the genomic DNA of whole blood in ACPA-positive RA cases. This method concentrated on a specific subset of DMS affected by single nucleotide polymorphisms (SNPs) associated with the disease. Notably, almost all identified DMS (9 out of 10) were situated within the HLA locus. However, it is crucial to acknowledge that the DNA methylation profile reflects numerous environmental factors and ongoing inflammation in RA patients, making it challenging to establish RA-specific causal relationships between these elements and DMS changes. Follow-up research has shown that the methylome of peripheral mononuclear cells can provide predictive insights into the progression from undifferentiated arthritis to RA, with these changes linked to various inflammatory pathways and transcription factors.

Moreover, several research teams have carried out epigenetic studies profiling particular cell subpopulations, revealing significant changes in the methylome of CD4 + memory cells in comparison to CD4 + naïve cells, specific regulation of the CTLA4 promoter triggered by methylation, and an increase in FOXP3 expression in regulatory T cells (Tregs). Additionally, there has been evidence supporting the epigenetic regulation of inflammatory cytokines in monocytes, alongside numerous immune-related pathways in fibroblast-like synoviocytes, especially in contrast to osteoarthritis within the framework of RA (Fig 4, [32]).

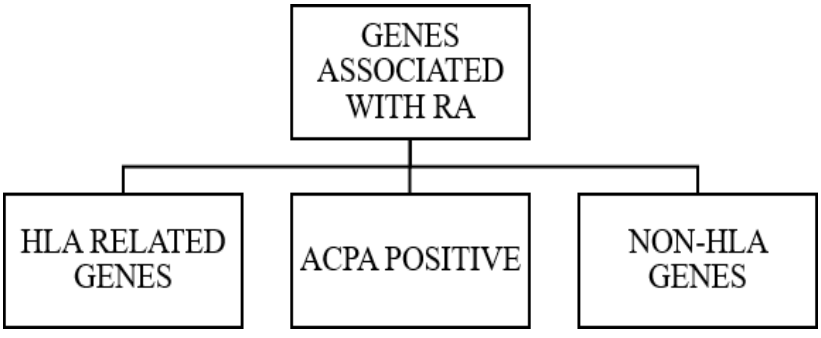

Fig. 4: Genes associated with RA

5.2. Lymphoma

The epigenetic repression of tumor suppressor and B-cell specific genes represents a significant mechanism in hematopoietic cancers. Genetic variations that affect methylation processes may contribute to lymphoma through hypo- or hypermethylation of proto- oncogenes or tumor suppressor genes, respectively, or by reactivating viruses. Deficiencies in folate or genetic differences in folate metabolism can alter DNA methylation patterns and disrupt DNA synthesis and repair processes. The enzyme 5,10-methylenetetrahydrofolate reductase (MTHFR), which is crucial in the folate metabolic pathway, catalyses the formation of 5-methyltetrahydrofolate—a principal donor of one-carbon units necessary for DNA synthesis and methylation. A single nucleotide polymorphism (SNP) in the MTHFR gene, which is linked to enzyme thermolability, might impede DNA methylation and redirect the flow of one-carbon units towards purine and DNA synthesis and repair. Similar findings have been observed for polymorphisms in the thymidylate synthase (TYMS) and methionine synthase (MTR) genes. TYMS is essential for maintaining adequate supplies of deoxynucleotides needed for DNA synthesis. Dysfunction in TYMS has been connected to chromosomal damage and the emergence of fragile sites. A polymorphic 28-base pair double (as opposed to triple) repeat in the promoter region and a 6-base pair deletion in the 3' UTR of the TYMS gene can inhibit TYMS gene expression and mRNA stability, potentially increasing the occurrence of DNA double-strand breaks and chromosomal translocations [34].

Research indicates that chronic inflammation could facilitate the neoplastic transformation of lymphocytes by enhancing the proliferation and survival of mutated cells via the activation of nuclear factor (NF)-κB and AP-1 response genes [35]. Perhaps the most significant non-Hodgkin lymphoma (NHL) risk alleles identified to date are SNPs in the tumor necrosis factor α (TNF-α) and interleukin (IL)10 genes [36]. TNF-α, primarily produced by mast cells, macrophages, and other immune cells, is a proinflammatory immunoregulatory cytokine and a crucial mediator of lymphocyte responses, natural killer cell functionality, and dendritic cell maturation. Increased TNF-α expression boosts the anti- apoptotic behavior in B-cells through NF-κB activation, leading to the induction of multiple anti-apoptotic factors, including members of the Bcl2 family, cellular inhibitors of apoptosis, and cell cycle regulators [37].

NOD2 and TLR4 act as pro-inflammatory mediators that are vital as the first defense line against viral and bacterial infections, offering non-specific protection against various pathogens. NOD2 directs antimicrobial action through an NF-κB-mediated pathway involving inflammation and apoptosis [38]. A rare CARD15 C insertion at nucleotide 1007 results in a premature stop codon that has been associated with autoimmune disorders like Crohn's disease and psoriasis, as well as an increased risk of lymphoma. The TLR4 gene promotes the release of pro-inflammatory cytokines by human cells in response to lipopolysaccharide and facilitates tolerance and B-cell activation. A TLR4 polymorphism (Asp299Gly) in the extracellular domain weakens receptor signaling and lowers IL-12 and IFNγ levels. The TLR4 299Gly allele has been inversely correlated with the risk of gastric MALT lymphoma. Additionally, an important innate immune response gene, the receptor for the Fc portion of immunoglobulin G (FCGR2A), has been linked to an elevated risk of NHL. The Arg variant may support lymphomagenesis due to impaired immunoglobulin G2- mediated phagocytosis and a promotion of antibody-driven inflammation [14].

Reactive oxygen species (ROS) are implicated in various inflammatory conditions and cancer risk (Fig 5, [39]). Phagocytic macrophages and neutrophils represent the initial inflammatory response against infectious agents and antigens. These cells undergo a respiratory burst, during which membrane-bound enzymes, NADPH-oxidase and nitric oxide

synthase (NOS), generate superoxide anion radicals and nitric oxide radicals. The Leu/Leu genotype of a non-synonymous SNP in the nitric oxide synthase gene (NOS2A Ser608Leu), found in a functionally relevant region, has been associated with gastric cancer and a 2 to 3-fold heightened risk for NHL [40]. The transformation of the superoxide anion into hydrogen peroxide occurs spontaneously or is facilitated by superoxide dismutase (SOD). The expression of the mitochondrial antioxidant enzyme manganese SOD (SOD2) is induced by pro-inflammatory cytokines such as IL-1 and TNF-α. The variant Ala allele of a non- synonymous SNP in SOD2 (Val16Ala), which enhances ROS scavenging, has been linked to a marginally increased risk of B-cell lymphomas [34].

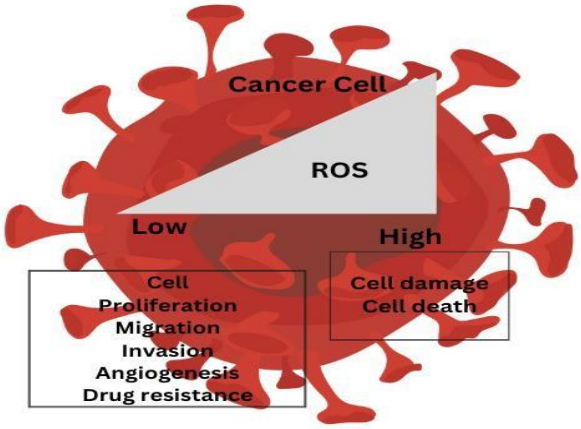

Fig 5: Role of ROS in cancer cell

An association between obesity and hematological-lymphopoietic cancers has been recognized, with elevated risks noted for NHL, leukemia, and multiple myeloma. Obesity is correlated with impaired immune function and systemic inflammation, characterized by increased circulation of pro-inflammatory mediators like leptin, TNF-α, IL-6, C-reactive protein, and decreased levels of the anti-inflammatory peptide ghrelin [34].

Other less obvious but significant genetic locations associated with lymphoma include SNPs in genes that affect the production and metabolism of sex hormones. Prolactin and estrogens, which play a crucial role in female reproduction, also act as immune modulators that influence apoptosis, immune cell activation and proliferation, and support the growth and survival of B-cells. Higher levels of prolactin have been linked to the advancement of hematological disorders like AML and NHL (Fig 6, [34]) [41].

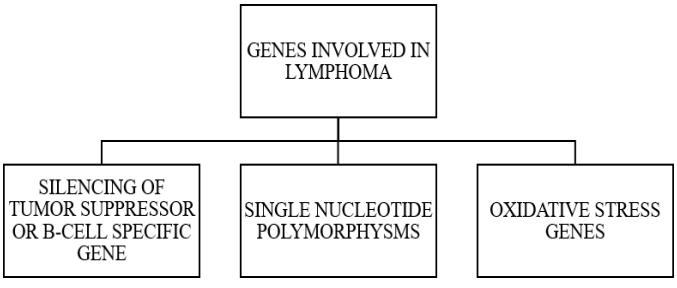

Fig. 6: GENES INVOLVED IN LYMPHOMA

6. GENETIC AND IMMUNE OVERLAPS IN RHEUMATOID ARTHRITIS AND LYMPHOMA

Rheumatoid arthritis (RA) and lymphoma are two intricate medical conditions that share common underlying processes, which include genetic predispositions, dysregulation of the immune system, chronic inflammation, and epigenetic changes. These overlapping pathways clarify the noted connection between RA and a heightened risk of developing lymphoma.

Genetic and Immune Dysregulation: Both RA and lymphoma have been linked to variations in significant immune-related genes, especially within the HLA region. In RA cases, genetic correlations mainly pertain to HLA-DRB1, which is crucial to the autoimmune features of the condition. In contrast, variations in genes such as TNF-α, IL-10, and TLR4 impact the risk of lymphoma and are essential for managing immune responses and inflammatory processes. The involvement of these genes in both disorders indicates a shared genetic vulnerability that affects immune system performance.

Chronic Inflammation: Chronic inflammation is a key characteristic of RA and significantly contributes to the onset of lymphoma. In RA, ongoing inflammation driven by cytokines like TNF-α and IL-6 activates immune cells and causes tissue damage. Similarly, these inflammatory mediators play a role in lymphomagenesis by promoting the survival and growth of immune cells, potentially leading to the malignant transformation of lymphocytes. Thus, the chronic inflammation associated with RA may create an environment favorable for the development of lymphoma.

Epigenetic Alterations and DNA Methylation: Epigenetic changes, particularly those involving DNA methylation, have been linked to both RA and lymphoma. In RA, changes in the DNA methylation patterns of immune-related genes contribute to disease progression and inflammation. In lymphoma, DNA methylation defects caused by polymorphisms in genes like MTHFR can impair DNA repair processes and promote tumor development. These epigenetic modifications may provide a connection between RA and lymphoma by affecting similar molecular pathways.

B-cell Involvement and Immune Activation: Dysregulated B-cell activation is evident in both RA and lymphoma. In RA, the generation of autoantibodies, such as rheumatoid factor and anti-citrullinated protein antibodies (ACPAs), reflects B-cell dysfunction that leads to joint inflammation. In lymphoma, specifically non-Hodgkin lymphoma (NHL), B-cell proliferation is a key feature of the disease. Genetic factors that influence B-cell survival, such as polymorphisms in TNF-α and Bcl2 family genes, might predispose individuals to both conditions, highlighting a shared immune activation pathway.

In conclusion, the genetic susceptibility, ongoing inflammation, epigenetic changes, and immune dysregulation featured in RA provide a biological basis for the increased lymphoma risk in those affected. A thorough understanding of these shared mechanisms is crucial for identifying potential therapeutic targets and improving the management of patients facing both RA and lymphoma [34]; [32].

7. DIAGNOSIS

The diagnosis of rheumatoid arthritis is mainly based on clinical evaluation. The typical manifestation is polyarticular, characterized by pain, stiffness, and swelling in multiple joints in a bilateral and symmetric manner. A small percentage of patients may show

oligoarticular involvement that is asymmetric. The onset is generally gradual, with joint symptoms developing over a period of weeks to months, often accompanied by symptoms such as anorexia, weakness, or fatigue. Patients typically experience morning stiffness that lasts for more than an hour [42].

Frequently affected joints include the wrists, proximal interphalangeal, metacarpophalangeal, and metatarsophalangeal joints, while the distal interphalangeal joints and spinal joints are usually not involved. Common examination findings encompass swelling, a boggy texture, tenderness, warmth, and muscle atrophy around the affected joints. Weakness tends to be more significant than the tenderness observed. In rare instances, patients may come in with a single joint being affected or present with severe systemic symptoms like fever, weight loss, lymphadenopathy, and involvement of multiple organs, such as the lung or heart.

C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) are commonly utilized clinical biomarkers to assess the overall inflammatory status in RA patients (Fig 7, [21]). CRP is an acute phase reactant made up of five 23-kDa subunits that belong to the pentraxin protein family. Its serum levels can rise significantly in response to infection, inflammation, or tissue damage, increasing by three or more orders of magnitude. This elevation is stimulated by the cytokines IL-6, IL-1, and TNF-α, with hepatocytes being the primary producers of CRP, although vascular smooth muscle cells, monocytes, lymphocytes, adipocytes, and neurons also contribute, albeit to a lesser extent. CRP levels are unaffected by factors such as age, gender, and abnormalities in erythrocytes and serum proteins, and studies have shown a positive correlation between CRP levels and disease activity, histological changes in the synovium, as well as radiological progression and various clinical factors including morning stiffness, pain, fatigue, grip strength, articular index, and disability. Hence, CRP has been identified as an important marker for diagnosing RA, as well as for tracking the progression of the disease and the prognosis regarding joint damage.

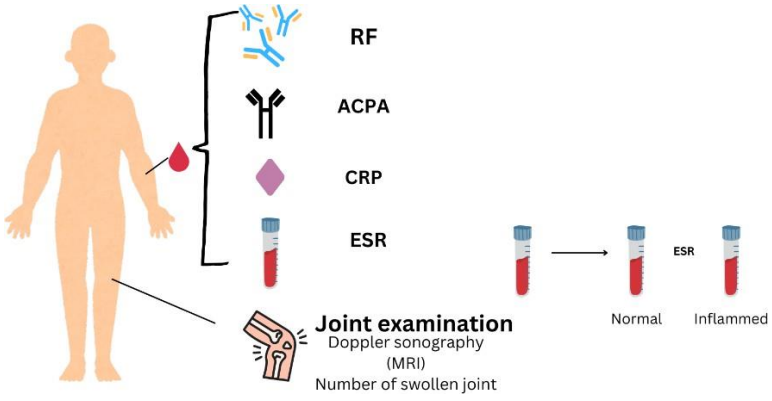

Fig 7: Diagnosis of RA

ESR is a commonly performed laboratory test that measures the rate at which erythrocytes settle in a blood sample contained in a test tube. When inflammatory processes, infections, autoimmune conditions like RA, pregnancy, anemia, certain kidney disorders, and some cancers such as lymphoma and multiple myeloma are present, elevated fibrinogen

levels in the blood lead to the clumping of red blood cells. This results in the formation of aggregates known as "rouleaux," which settle more quickly in the test tube due to their increased density [21].

The requirement for further evaluations, such as additional laboratory tests or functional imaging with FDG-PET, is partially contingent on the specific diagnosis and clinical presentation. In contemporary practice, lymphoma staging is predominantly “clinical,” relying on the previously mentioned evaluations, with or without additional noninvasive assessments to ascertain the disease's extent. The “pathologic” stage is determined through one or more invasive staging methods, like staging laparoscopy, which is infrequently conducted today. The stage is categorized according to the Ann Arbor staging system, which was later modified at the Cotswolds meeting in 1989. Unlike most solid tumor cancers, the stage of lymphoma has limited prognostic value. Stage IV disease is often observed in many cases of indolent B cell non-Hodgkin lymphoma due to bone marrow

Table 1: Stages of Lymphoma

STAGE	EXPLANATION OF THE DISEASE DERIVED FROM POSITRON EMISSION TOMOGRAPHY/COMPUTED TOMOGRAPHY (PET/CT) RESULTS.
I	Single nodal group or single extralymphatic lesion
II	Multiple nodal groups on same side of diaphragm or with limited contiguous extralymphatic involvement
III	Multiple nodal groups on both sides of the diaphragm; may involve the spleen
IV	Non-contiguous extralymphatic involvement

Hodgkin’s lymphoma is staged using the Cotswolds modification of the Ann Arbor system, classified as “early” for nonbulky stage I–II and “advanced” for stage III–IV, including bulky disease (Table 1, [43]). Chest x-rays and CT scan are necessary to assess disease bulk. Due to advancements in treatment, around 85% of patients achieve prolonged disease-free survival. Management depends on the disease stage, prognostic indicators, toxicity risks, and treatment response [44].

8. TREATMENTS PLANS

The typical treatment for individuals with rheumatoid arthritis has involved the use of non-steroidal anti-inflammatory medications. While these medications alleviate symptoms and signs, they have minimal impact on the structural advancement and long-term disability associated with rheumatoid arthritis. The most frequently prescribed disease-modifying antirheumatic agents included gold, penicillamine, and sulfasalazine, all of which resulted in

a gradual response along with significant toxicity. A preliminary study indicated that high doses of anti-TNF-α were beneficial for six months, but the effects diminished after discontinuing the treatment [45].

Non-steroidal anti-inflammatory drugs (NSAIDs) such as aspirin, diclofenac, or ibuprofen effectively alleviate pain and swelling while enhancing joint function, but they do not modify the disease; hence, they do not stop further joint damage. Disease-modifying anti-rheumatic drugs (DMARDs) target inflammation linked to rheumatoid arthritis and help prevent any further damage to the joints. By definition, DMARDs are medications that, unlike those that do not halt disease progression (such as NSAIDs or pain relievers), address the signs and symptoms of rheumatoid arthritis, enhance physical function, and prevent the advancement of structural joint damage. The existing DMARDs are categorized into three groups: (1) conventional synthetic DMARDs (like methotrexate, hydroxychloroquine, and sulfadiazine), (2) targeted synthetic DMARDs (such as pan-JAK and JAK1/2 inhibitors), and
(3) biologic DMARDs (including TNF inhibitors, TNF receptor inhibitors, IL-6 inhibitors, IL-6R inhibitors, B cell depleting antibodies, and inhibitors of co-stimulatory molecules) [21].

The standard treatment regimen for Hodgkin lymphoma is ABVD (Adriamycin, bleomycin, vinblastine, and dacarbazine) whereas the treatment options for non-Hodgkin lymphoma differ depending on the specific histology, but frequently include regimens like CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) with or without rituximab (Rituxan; R-CHOP), a monoclonal antibody targeted at CD20-positive B lymphocytes [43].

Several new treatment alternatives, such as cytokines like interferon alfa (IFN-), monoclonal antibodies (whether unconjugated or linked with radioisotopes or toxins), and purine analogues are currently under exploration and have the potential to alter the natural progression of these indolent lymphomas. Additionally, radioimmunotherapy using conjugated monoclonal antibodies is being studied. Purine analogues present a distinct mechanism of action and have demonstrated notable response rates in individuals with indolent lymphomas [46]. Additionally, other agents such as bendamustine (Bendeka), an alkylating agent, and lenalidomide (Revlimid) are commonly employed in various treatments for non-Hodgkin lymphoma [43].

9. CONCLUSION

RA is a multifaceted autoimmune disorder that is shaped by a combination of genetic, biological, and environmental factors, which in turn elevate the risk of developing lymphoma, particularly non-Hodgkin lymphoma (NHL). Upcoming treatments for RA ought to concentrate on targeted therapies that control inflammation and reduce the risk of lymphoma. By leveraging genetic information personalized treatments can be done that alleviate RA symptoms and tackle associated immune challenges. Innovations in drug development could result in efficient therapies. Key questions for future research endeavours include:

1) How can pharmacological therapies be tailored to simultaneously address the persistent inflammation in RA and the immune dysfunction linked to lymphoma?
2) What novel drug targets could potentially be identified to prevent the onset of lymphoma in patients with RA?

3) Additionally, how can existing biologics be refined to reduce the risk of lymphoma while still effectively managing joint inflammation.

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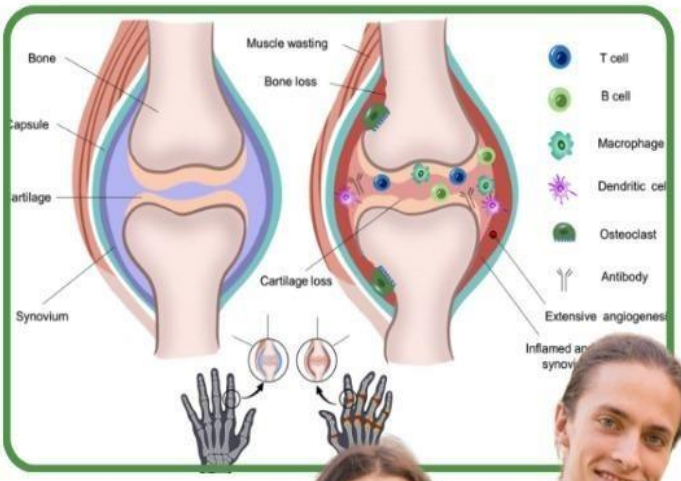

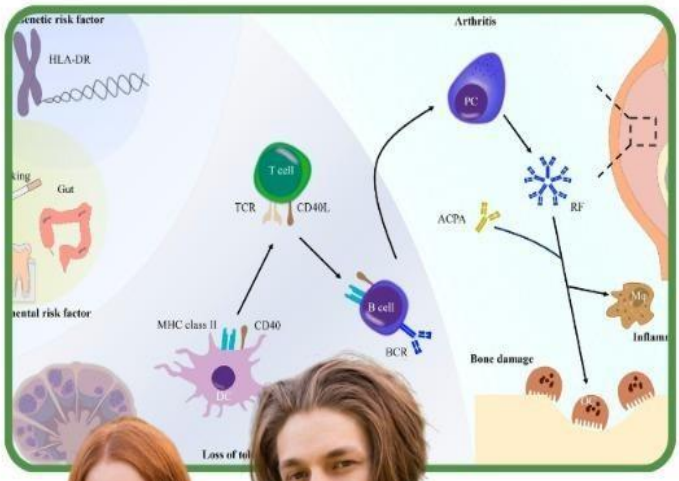

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