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Review Article

A CRITICAL REVIEW OF CHRONIC INFLAMMATION: PATHOGENESIS, CELLULAR MECHANISMS, TISSUE REMODELING AND CLINICAL IMPLICATIONS

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ABSTRACT

Chronic inflammation is a persistent inflammatory response characterized by prolonged activation of innate and adaptive immune mechanisms, ongoing tissue injury, and simultaneous attempts at repair. Unlike acute inflammation, which is typically short-lived and dominated by neutrophilic infiltration, chronic inflammation may persist for weeks, months or years and is characterized histologically by mononuclear cell infiltration, including macrophages, lymphocytes, and plasma cells, together with tissue destruction, angiogenesis, fibrosis, and remodeling. Chronic inflammation is central to the pathogenesis of numerous infectious, autoimmune, metabolic, degenerative, and neoplastic diseases. The mechanisms underlying chronic inflammation are complex and involve interactions between immune cells, stromal cells, endothelial cells, extracellular matrix components, and a wide range of inflammatory mediators. Macrophages occupy a central position in this process, T lymphocyte and B lymphocytes further regulate the inflammatory response through cytokine production and antibody-mediated mechanisms. Recent evidence has established chronic inflammation as a major biological link between infection, obesity, metabolic syndrome, cardiovascular disease, neurodegeneration, IBD, Chronic pulmonary disorders, and cancer. From a pathological perspective, recognizing the morphological patterns and underlying mechanisms of chronic inflammation is essential for diagnosis, prognosis, and therapeutic decision-making. This critical review discusses the cellular and molecular mechanisms of chronic inflammation, its morphological characteristics, major pathological patterns, mechanisms of tissue injury and repair, relationship with fibrosis and carcinogenesis, and emerging therapeutic approaches. A better understanding of chronic inflammation may facilitate the development of targeted strategies to control persistent inflammation while preserving beneficial host defence and tissue repair.

KEYWORDS: Chronic inflammation; macrophages, lymphocytes,cytokines, fibrosis, tissue remodeling; oxidative stress.

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1. INTRODUCTION

Inflammation is a fundamental biological response to tissue injury, infection, or cellular stress. It is traditionally classified into acute and chronic inflammation based on the duration, cellular composition, and pathological consequences of the inflammatory response. Acute inflammation generally develops rapidly and is characterized by vascular changes and recruitment of neutrophils. In contrast, chronic inflammation is a prolonged process in which inflammation, tissue injury, and repair occur simultaneously.

Chronic inflammation may develop following unresolved acute inflammation or may begin insidiously in response to persistent low-grade stimuli. These stimuli include microbial infections, autoimmune reactions, prolonged exposure to toxic substances, foreign materials, metabolic abnormalities, and persistent tissue stress. In many conditions, chronic inflammation becomes self-sustaining through a complex network of cytokines, chemokines, growth factors, lipid mediators, and intracellular signaling pathways.

The pathological significance of chronic inflammation extends far beyond local tissue injury. Persistent inflammatory signaling may induce fibrosis, vascular remodeling, genomic instability, metabolic dysfunction, and alteration in the tissue microenvironment. Increasing

evidence also demonstrates that chronic inflammation plays a crucial role in tumor initiation, progression, invasion, and metastasis.

From a pathology perspective, chronic inflammation represents not merely a collection of inflammatory cells but a dynamic interaction between immune responses and tissue remodeling. This review focuses on the mechanisms that maintain chronic inflammation and the morphological consequences of the prolonged inflammatory state.

2. DEFINITION AND CHARACTERISTICS OF CHRONIC INFLAMMATION

Chronic inflammation can be defined as a prolonged inflammatory response in which active inflammation, tissue destruction, and repair occur concurrently.

The classical pathological features include:
1. Infiltration by mononuclear inflammatory cells.
2. Predominance of macrophages, lymphocytes, and plasma cells.
3. Ongoing tissue destruction.
4. Angiogenesis and vascular remodeling.
5. Fibroblast activation and collagen deposition.
6. Progressive fibrosis and tissue remodeling.

The severity and pattern of chronic inflammation vary according to the underlying cause, affected organ, host immune response, and duration of disease.

3. ETIOLOGY OF CHRONIC INFLAMMATION

3.1 Persistent infections

Microorganisms that are difficult to eradicate may produce chronic inflammation. Examples include:
Mycobacterium tuberculosis, mycobacterium leprae, cetain fungi, persistent viral infections, chronic parasitic infections.
These organisms may survive within tissues or macrophages and stimulate prolonged immune responses.

3.2 Autoimmune diseases

In autoimmune disorders, immune responses are directed against self-antigens. Examples include:
Rheumatoid arthritis, Systemic lupus erythematosus, Autoimmune thyroiditis, inflammatory bowel disease, autoimmune hepatitis.
Persistent activation of T and B lymphocytes contributes to progressive tissue damage.

3.3 Prolonged exposure to toxic substances

Long-term exposure to exogenous or endogenous irritants may induce chronic inflammation. Examples include: Silica, asbestos, tobacco smoke, air pollutants, crystalline substances

3.4 Metabolic disorders

Metabolic abnormalities can produce low-grade chronic inflammation, often referred to as metaflammation.
Important associations include:
Obesity, Type 2 diabetes mellitus, metabolic syndrome, non-alcoholic fatty liver disease, atherosclerosis

3.5 Foreign bodies

Foreign materials that resist degradation can include chronic inflammatory responses. Examples include:
Sutures, prosthetic materials, splinters, talc, silica particles

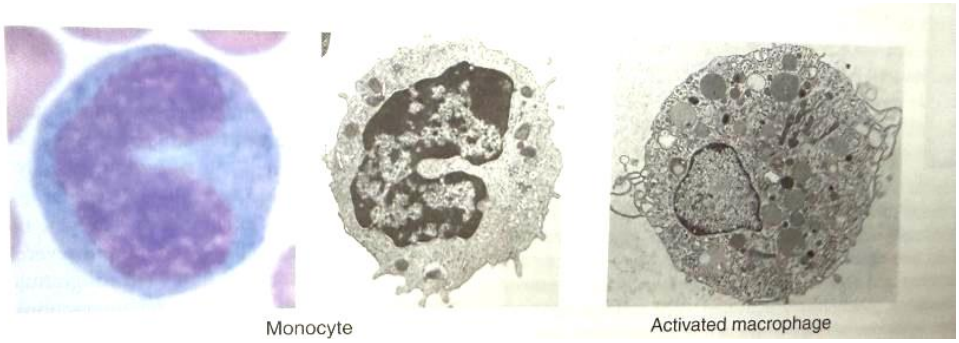
Foreign-body giant cells may develop as a consequence of macrophage fusion.

4. CELLULAR COMPONENTS OF CHRONIC INFLAMMATION

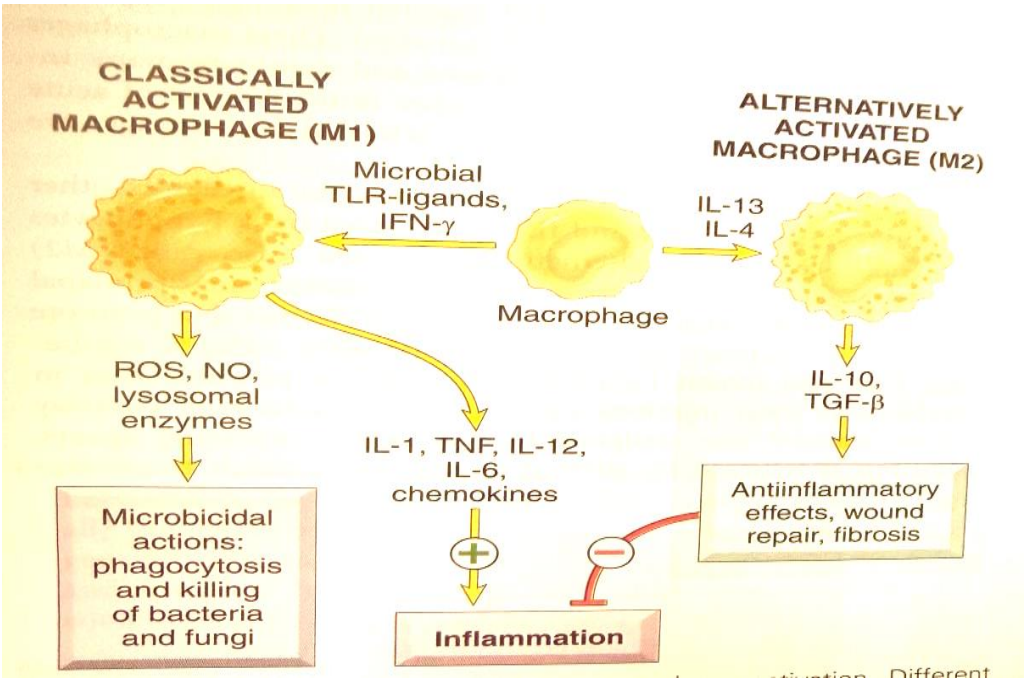
4.1 Macrophages

Macrophages are the principal effector cells of chronic inflammation. They arise from circulating monocytes, tissue-resident macrophages populations. Macrophages have multiple functions including phagocytosis, antigen presentation, cytokine secretion, production of reactive oxygen species, tissue repair, fibrosis and regulation of angiogenesis.
M1-like macrophages are generally associated with microbial killing, pro-inflammatory cytokine production and tissue injury.
M2-like macrophages are associated with tissue repair, angiogenesis, fibrosis and immunomodulation

In vivo, macrophages phenotypes exist along a continuous spectrum rather than as two strictly separate populations.



The morphology of monocyte and activated macrophages



Classical and alternative macrophage activation. Different stimuli activate tissue macrophages to develop into functionally

Distinct populations. Classically activated (M1) macrophages are induced by microbial products and cytokines, particularly IFN-. They pahgocytose and destroy microbes and debris from dead tissues and can potentiate inflammatory reactions.

Alternatively activated (M2) macrophages are induced by other cytokines and are important in tissue repair and the resolution of inflammation.

4.2 Lymphocytes

Lymphocytes are important regulators of chronic inflammation.

T. lymphocytes: CD4+ T-helper cells can be divided into functional subsets-

T-cell subset	Major cytokines	Major function
Th1	IFN-Y, TNF	Macrophage activation and cellular immunity
Th2	IL-4, IL-5, IL-13	Allergy, eosinophilic inflammation, fibrosis
Th17	IL-17, IL-22	Neutrophilic inflammation and mucosal immunity
Treg	IL-10, TGB-β	Immune suppression and tolerance

B lymphocytes and plasma cells

B cells contribute to chronic inflammation through antibody production, antigen presentation, cytokine secretion and formation of ectopic lymphoid structures.
Plasma cells may be prominent in chronic infections and autoimmune diseases.

4.3 Eosinophils

Eosinophils are particularly important in allergic disorders, parasitic infections, certain drug reactions and eosinophilic gastrointestinal diseases. Their granules contain cytotoxic proteins capable of producing tissue injury.

4.4 Mast cells

Mast cells participate in both acute and chronic inflammatory responses. They release histamine, proteases, leukotrienes, prostaglandins and cytokines. They contribute to allergic inflammation, vascular changes, fibrosis and tissue remodeling.

4.5 Neutrophils

Although neutrophils are classically associated with acute inflammation, they may persist in certain chronic inflammatory conditions. Persistent neutrophilic inflammation is observed in chronic obstructive pulmonary disease, brochiectasis, chronic bacterial infections and some inflammatory bowel diseases.

Neutrophil extracellular traps (NETs) have also emerged as important contributors to chronic inflammation and thrombosis.

5. MOLECULAR MECHANISMS OF CHRONIC INFLAMMATION

Chronic inflammation of regulated by interconnected molecular pathways.

5.1 Nuclear factor-kB pathway
It is a major transcription factor regulating inflammatory gene expression. Activation results in increased production of TNF, IL-1, IL-6, chemo kines and adhesion molecules.
Persistent NF-kB activation contributes to chronic inflammatory diseases and cancer.

5.2 Inflammasomes
They are intracellular multi protein complexes that detect cellular stress and danger signals. Inflammasomes activation leads to caspase-1 activation and maturation of IL-1β and IL-18.

5.3 Reactive oxygen and nitrogen species
Activated inflammatory cells produce reactive oxygen species and reactive nitrogen species. These molecules contributes to DNA damage, lipid peroxidation, protein modification, mitochondrial dysfunction and cellular injury. Persistent oxidative stress may contribute to carcinogenesis and degenerative disease.

5.4 Cytokine signaling
Major cytokines involved in chronic inflammation include TNF, IL-1, IL-6, IL-17, IFN-Y, TGB-β. These mediators regulate leukocyte recruitment, immune activation, tissue injury, and fibrosis.

6. MORPHOLOGICAL PLATTERND OF CHRONIC INFLAMMATION
The microscopic appearance depends on the underlying etiology.

6.1 Chronic nonspecific inflammation
Characterized by lymphocytes, plasma cells, macrophages, fibrosis and tissue destruction

6.2 Granulomatous inflammation
Granuloma are organized collections of activated macrophages, often surrounded by lymphocytes. They may be caseating, non-caseating and foreign-body type. Common causes are tuberculosis, sarcoidosis, fungal infections, crohn disease and foreign-body reactions.

Granulomas are induced by
- Certain chemicals (lipids, complex polysaccharides)
- Indigestible materials (sutures, cholesterol crystals, foreign bodies) and
- Some organisms (tubercle bacillus, fungi) along with an element of cell-mediated immunity.

Foreign Body Granuloma
- Foreign body granuloma is usually due to particulate crystalline matter, which may be immunologically inert.
- The foreign material is seen within or enclosed by giant cells.
- Foreign body giant cells are formed by fusion of histocytes and have numerous nuclei, scattered histocytes and have numerous uniform nuclei, scattered in a large amount of cytoplasm.
- The foreign body may be identifiable (e.g. suture, vegetable matter, crystals, fungus etc.) or be dissolved during tissue processing and hence be represented by cleft-like spaces (e.g. cholesterol).

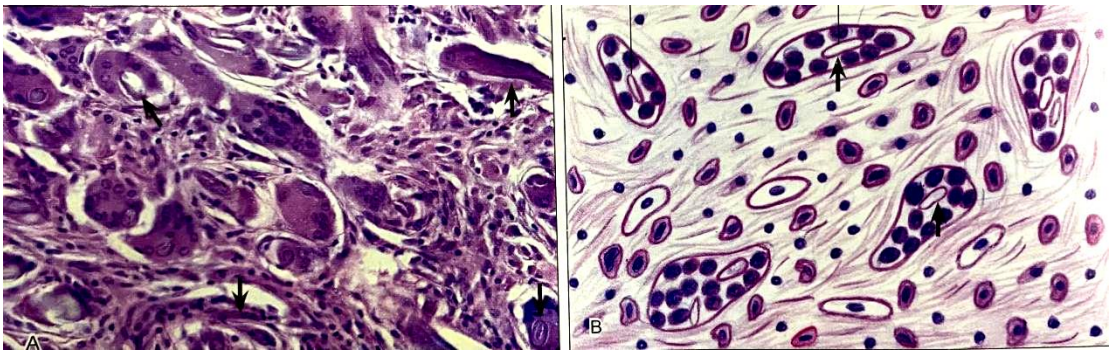


Fig. A and B: Foreign body giant cell granuloma with suture material in many foreign body giant cells.

Tuberculous Granuloma
- In tuberculous granuloma, cell-mediated immunity plays a major role.
- Hence, macrophage activation by lymphokines is prominent, transforming them into epitheliod cells- large often polygonal cells, with abundant pink cytoplasm and vesicular nucleus.
- They fuse to form Langhan's giant cells, classically with nuclei arranged peripherally; or at the poles of the cells.
- Tuberculoid granulomas are also seen in sarcoidosis, tuberculoid leprosy, berylliosis and some fungal infections.
- Tuberculosis can be distinguished from the above by the presence of characteristic caseous necrosis (tissue destruction) in the centre yielding a granular featureless amorphous eosinophilic debris.
- However, it should be confirmed by acid-fast staining for the tubercle bacillus (or by culture, serological studies etc.).

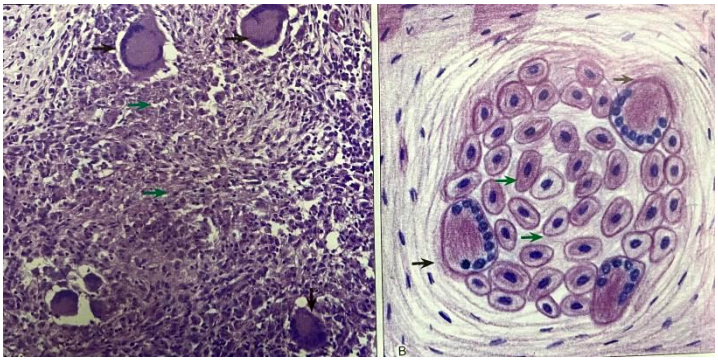


Fig A and B: Epitheliod cells and Langhan's giant cells in a tubercular granuloma. Nuclei in the Langhan giant cell are arrannged in "horse shoe" like pattern.

Xanthogranuloma

Granuloma formed in response to lipid-rich material (as in hyperlipidaemias) have collections of foamy histocytes - large, with pale to faintly granular cytoplasm. These are called Xanthogranulomas. Giant cells are fewer and may have a central dense cytoplasm surrounded by a ring of nuclei and peripheral foamy cytoplasm (Touton giant cells).

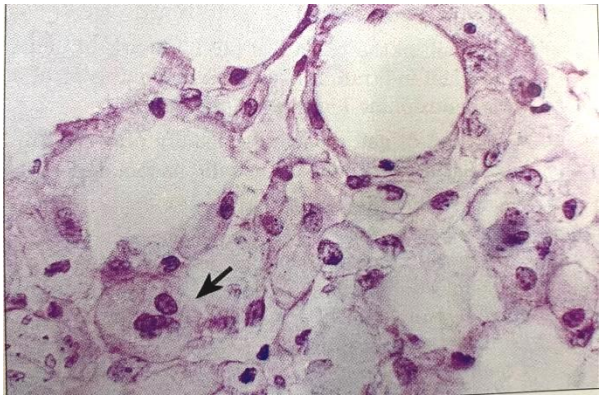


Fig. Lipophages and Touton giant cells (arrow) in inflammed adipose tissue.

6.3 Chronic suppurative inflammation

This pattern is characterized by persistent neutrophilic infiltration and tissue destruction. Examples include: chronic abscess, osteomyelitis, bronchiectasis.

6.4 Fibrosing inflammation

Persistent inflammation stimulates fibroblast activation and extracellular matrix deposition. This may result in organ fibrosis, architectural distortion and loss of normal function

7. CHRONIC INFLAMMATION AND TISSUE REPAIR

Inflammation and tissue repair are closely interconnected. Growth factors released by macrophages and other cells stimulate:

Fibroblast proliferation, collagen synthesis, angiogenesis, extracellular matrix remodeling

Important mediators include: TGF-β, PDGF, VEGF,FGF

When repair mechanisms become excessive or dysregulated, fibrosis develops.

The pathological consequences of fibrosis include:

Loss of normal tissue architecture, reduced organ compliance, impaired organ function, progressive organ failure

8. CHRONIC INFLAMMATION AND FIBROSIS

Fibrosis represents one of the most important long-term consequences of chronic inflammation. Major fibrotic disorders include:

Liver cirrhosis, pulmonary fibrosis, renal interstitial fibrosis, cardiac fibrosis, systemic sclerosis

TGF-β is a central profibrotic mediator. It promotes fibroblast activation and extracellular matrix deposition.

The interaction between immune cells and fibroblasts is increasingly recognized as an important determinant of chronic disease progression.

9. CHRONIC INFLAMMATION AND CANCER

The relationship between inflammation and cancer is complex and bidirectional. Chronic inflammation may promote carcinogenesis through:

1. DNA damage caused by reactive oxygen species.
2. Increased cellular proliferation.
3. Activation of pro-survival signaling pathways.
4. Angiogenesis
5. Immune evasion
6. Remodeling of the tumor microenvironment.

Examples include

. Chronic hepatitis → hepatocellular carcinoma

. Helicobacter pylori-associated gastritis → gastric carcinoma

. Chronic inflammatory bowel disease → colorectal carcinoma

. Chronic pancreatitis → pancreatic carcinoma

Tumor-associated macrophages may promote tumor growth, angiogenesis, invasion, and metastasis.

Thus, chronic inflammation may create a microenvironment favorable to malignant transformation and progression.

10. CHRONIC INFLAMMATION IN MAJOR DISEASES

Cardiovascular disease

Chronic inflammation plays a central role in atherosclerosis. Monocyte recruitment, macrophage activation, lipid accumulation, and inflammatory cytokines production contribute to plaque formation and progression.

Metabolic disease

Obesity-associated inflammation involves adipose tissue macrophages, adipokines, and inflammatory cytokines. This contributes to insulin resistance and metabolic dysfunction.

Chronic lung disease

Persistent inflammation contributes to airway remodeling and progressive loss of lung function in chronic respiratory disorders.

Neurodegenerative disease

Microglial activation and neuroinflammation have been implicated in several neurodegenerative diseases.

Gastrointestinal disease

Chronic inflammation contributes of inflammatory bowel disease, chronic gastritis, chronic pancreatitis, and other disorders.

Inflammation may follow a chronic (protracted) course under several situations;

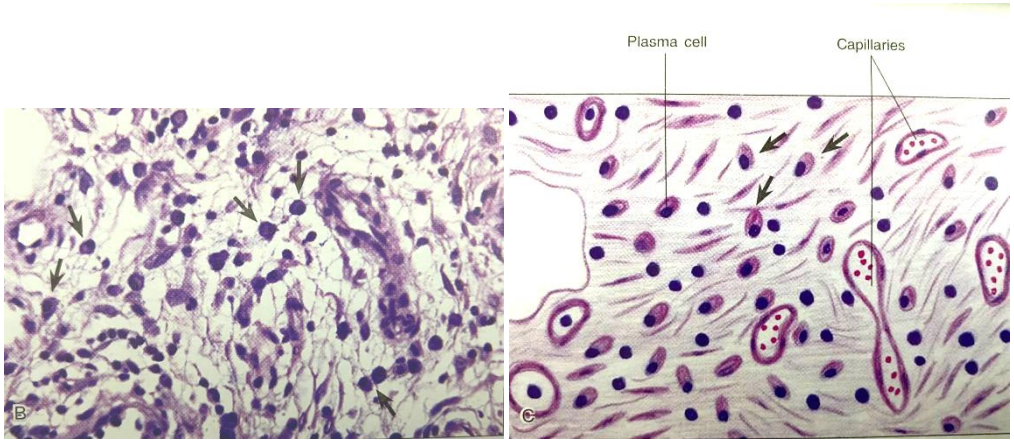
(a) Following acute inflammation if irritant stimulus persists or if debridement and healing are hampered (e.g., Peptic ulcer, infective immune response or therapy in bacterial infections, enclosed tissue debris as in an abscess, splinters or shrapnel in wound, dead bone spicules in osteomyelitis);

(b) Repeated bouts of acute inflammation as in chronic cholecystitis, chronic pyelonephritis or

(c) Insidiously as chronic inflammation per se. This could be due to low virulent organisms or non-degradable material that resists digestion. An associated element of immune reaction may play a variable role (e.g., tuberculosis, viral and fungal infections, cholesterol-rich exudates, foreign bodies like asbestos and silica in the lungs, rheumatoid arthritis and other autoimmune diseases).

Histologically, chronic inflammation is characterized by inflammation and healing going on simultaneously.

Inflammation is represented by predominantly mononuclear cells, i.e., lymphocytes, histocytes and plasma cells.



B&C Chronic inflammatory granulation tissue shows capillaries, lymphocytes, plasma cells with eccenteric nuclei with cartwheel nuclear chromatin and some neutrophils.

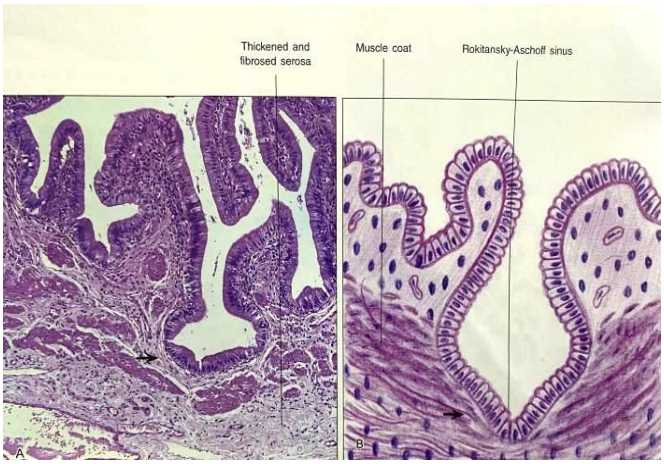
Chronic Cholecystitis

In chronic cholecystitis, the gall bladder is grey white in colour and the wall is thickened from 2 mm to 1 cm, depending upon the amount of fibrosis. Mucosa may be ulcerated. Gall bladder may demonstrate single cholesterol/multifaceted mixed stones/pigment stones.

Chronic cholecystitis with gall stones in lumen. Thick fibrosed wall and loss of mucosal villi.

Microscopically,

- Gall bladder is identified by the absence of muscularis mucosa in a hollow organ with tall columnar mucus-secreting cells lining the villi.
- Mononuclear infiltrates are seen in all coats.
- Cholesterol, if reabsorbed, is phagocytosed by macrophages in mucosa cholestrolosis.
- Serosa shows fibrosis and the wall may be markedly thickened.



Chronic cholecystitis - Inflammation and fibrosis in muscle coat with Rokinansky-Aschoff sinus

Chronic Gastric Ulcer

In chronic gastric ulcer, grossly, the stomach or gastrectomy specimen is recognized by being a viscus organ. The ulcer is recognized as an ulcer crater on the mucosal aspect. In chronic ulcer, mucosal folds radiate towards the ulcer.

Chronic gastric ulcer. Ulcer crater with converging rugae towards the ulcer are seen.

Microscopically

- Stomach is identified by the four coats and mucosa is thick, formed of closely packed glands, chief and parietal cells and the surface gastric pits with mucus-secreting cells.
- The ulcer is deep, with its floor covered by a thin zone of debris and an acute inflammatory zone of neutrophils.
- Deep to that are the zones of granulation tissue and the dense fibrous scar tissue.

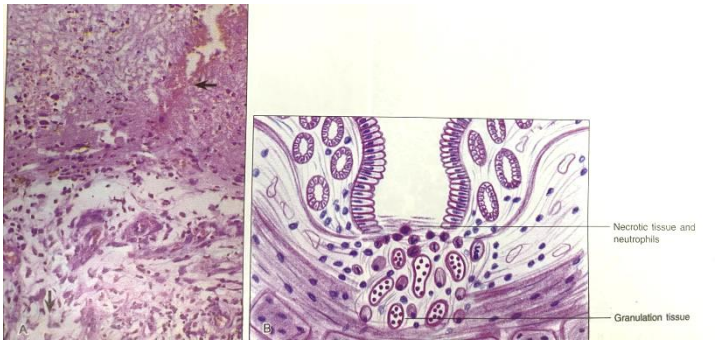


Fig. A & B: Chronic gastric ulcer - base with necrotic exudate (←) and Granulation tissue zone (bottom).

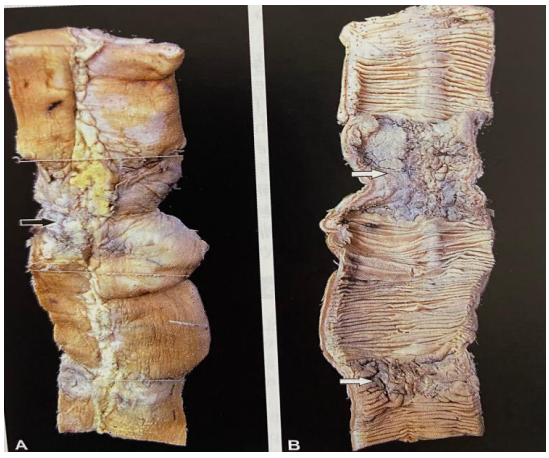
Tuberculosis Intestine

Intestinal tuberculosis occurs in 3 forms: primary, secondary and hyperplastic. Secondary tuberculosis of small intestine is most common.

Gross More often, the small intestine shows large ulcers which are transverse to the long axis of the bowel. These ulcers may be coated with caseous material. Advanced cases show transverse fibrous strictures and intestinal obstruction.

Microscopy

i. Presence of caseating tubercles in all the layers of intestine.
ii. Ulceration of mucosa with slough on the surface.
iii. Variable fibrosis in the muscular layer.



Intestinal tuberculosis. A, The external surface shows strictures and cut section of lymph node showing Caseation necrosis (Black arrow). B, The lumen shows transverse ulcers and strictures (arrows). The Intestinal wall has multiple transverse strictures where the intestinal wall is thickened and grey-white And mucosa over it is ulcerated.

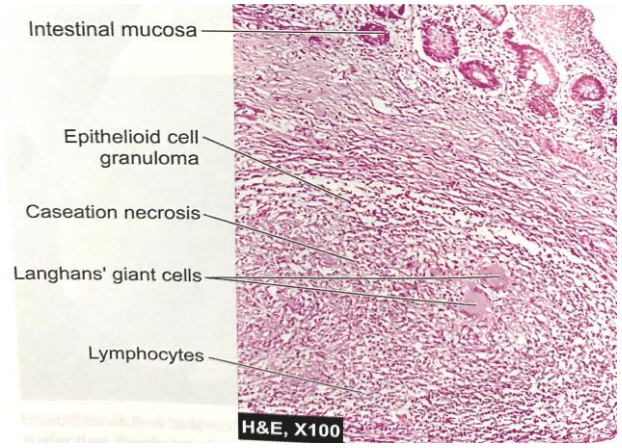


Fig. Tuberculosis of Intestine. The wall of Intestine Shoes Caseating Epitheliod Cell Granulomas.

11. EMERGING CONCEPTS

11.1 Trained immunity

Trained immunity describes the capacity of innate immune cells to develop long-lasting functional changes after exposure to certain stimuli.

This process involves epigenetic programming, metabolic changes, enhanced inflammatory responses. Trained immunity may contribute to persistent inflammation and vascular disease.

11.2 Immunometabolism

Immune cell function is closely linked to cellular metabolism. Inflammatory macrophages often demonstrate increased glycolytic activity, whereas reparative macrophage states may rely more heavily on oxidative metabolism. The relationship between metabolism and inflammation provides new opportunistic for therapeutic intervention.

11.3 Resolution of inflammation

Resolution is now recognized as an active biological process rather than simply the passive disappearance of inflammatory mediators. Specialized pro-resolving mediators are lipoxins, resolvins, protectins, maresins etc. These mediators may help terminate inflammation and restore tissue homeostasis.

12. DIAGNOSTIC APPROACH IN PATHOLOGY

The diagnosis of chronic inflammation relies on integration of clinical, radiological, microbiological, biochemical, and histopathological findings.

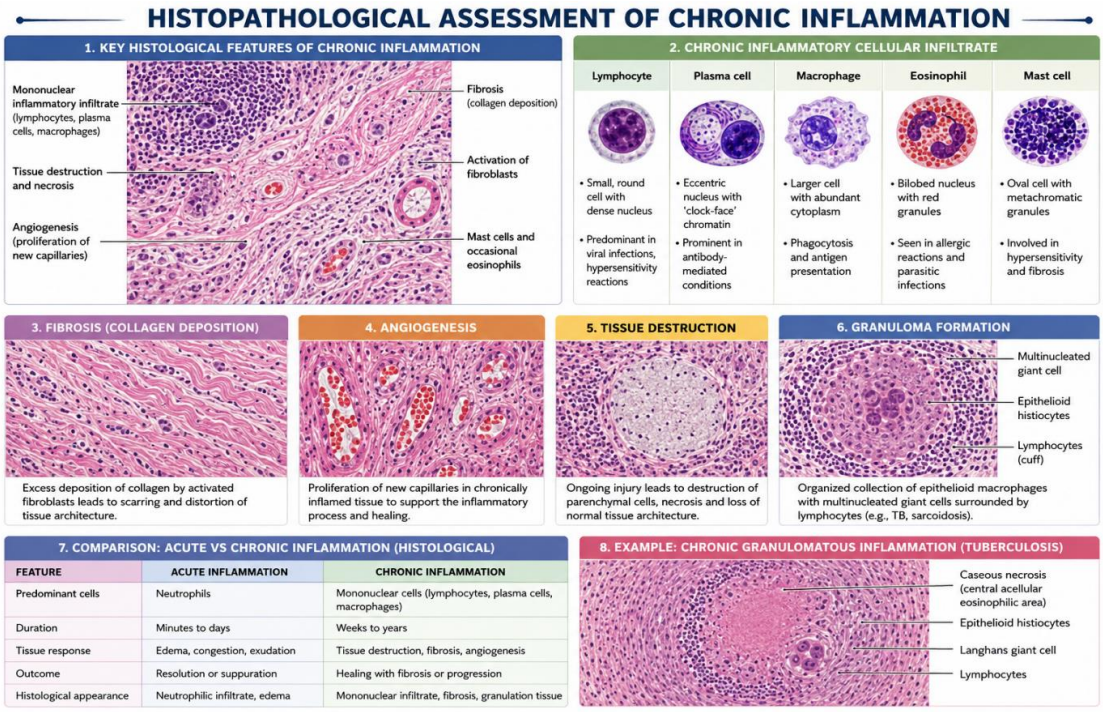
Histopathological assessment should include

1. Type and distribution of inflammatory infiltrate
2. Presence of granulomas
3. Degree of tissue destruction
4. Fibrosis and extracellular matrix deposition
5. Vascular changes
6. Presence of microorganisms
7. Evidence of dysplasia or malignancy

Special stains and ancillary investigations may include

- Ziehl-Neelsen stain
- Periodic acid-Schiff stain
- Grocott methenamine silver stain
- Gram stain
- Immunohistochemistry
- Molecular microbiological tests

The pathological diagnosis should always be interpreted in the clinical context.



13. THERAPEUTIC IMPLICATIONS

Treatment of chronic inflammation should ideally target the underlying cause rather than suppress inflammation indiscriminately.

Therapeutic approaches include:

- Eradication of persistent infection
- Immunomodulatory therapy
- Anti-inflammatory drugs
- Biologic agents targeting specific cytokines
- Lifestyle modification
- Metabolic disease management
- Antifibrotic therapies

Targeted therapies against TNF, IL-6, IL-17, IL-23, and other pathways have significantly changed the management of several inflammatory diseases.

However, excessive suppression of inflammation may increase susceptibility to infection and impair tissue repair. The future of treatment is likely to involve personalized modulation of inflammatory pathways based on disease mechanisms and patient-specific immune profiles.

14. ACUTE VERSUS CHRONIC INFLAMMATION

Feature	Acute inflammation	Chronic inflammation
Onset	Rapid	Slow or persistent
Duration	Hours to days	Weeks to years
Predominant cells	Neutrophils	Macrophages, lymphocytes, plasma cells
Tissue injury	Usually limited	Progressive
Fibrosis	Usually absent	Common
Angiogenesis	Limited	Prominent
Repair	Follows inflammation	Occurs simultaneously
Typical causes	Trauma, acute infection	Persistent infection, autoimmunity, metabolic disease

15. MAJOR MEDIATORS OF CHRONIC INFLAMMATION

Mediator	Major source	Principal effect
TNF	Macrophages, T cells	Inflammation, endothelial activation
IL-1	Macrophages	Fever, leukocyte recruitment
IL-6	Macrophages, stromal cells	Acute-phase response
INF-Ɣ	T cells, NK cells	Macrophage activation
IL-17	Th17 cells	Neutrophil recruitment
TGB-β	Macrophages, platelets, stromal cells	Fibrosis and immunoregulation
VEGF	Macrophages, endothelial cells	Angiogenesis
ROS	Neutrophils, macrophages	Oxidative tissue injury

16. CRITICAL PERSPECTIVE

The traditional concept of chronic inflammation as a static accumulation of mononuclear cells is increasingly inadequate. Modern research demonstrate that chronic inflammation is a dynamic process involving immune cells, metabolism, epigenetic regulation, tissue-resident cells, extracellular matrix, microbiota, and systemic metabolic factors.

The classical M1/M2 macrophage paradigm, although useful for teaching, does not adequately describe the complex spectrum of macrophages states observed in human disease. Similarly, the distinction between inflammation and repair is becoming less clear, as the same cellular populations may participate in both tissue injury and regeneration depending on their micro environment.

A major challenge is determining when inflammation is protective and when it becomes pathological. Inflammation is essential activation can cause progressive organ damage. Therefore, future therapeutic strategies should focus not only on suppressing inflammatory mediators but also on restoring immune homeostasis and promoting appropriate resolution.

The concept of resolution biology represents an important shift in therapeutic thinking. Rather than broadly inhibiting the immune response, future treatments may selectively promote endogenous mechanism that terminate inflammation while preserving antimicrobial and reparative functions.

17. CONCLUSION

Chronic inflammation is a complex, multi factorial pathological process characterized by persistent immune activation, tissue injury, and simultaneous repair. It plays a central role in the pathogenesis of infections, autoimmune, metabolic, cardiovascular, degenerative, fibrotic, and malignant diseases.

Macrophages, lymphocytes, cytokines, inflammasomes, oxidative stress, and tissue-related cells form an interconnected network that determines the progression and outcome of chronic inflammation. Persistent inflammatory signaling may result in fibrosis, organ dysfunction, and carcinogenesis.

For pathologists, recognition of the cellular composition and morphological patterns of chronic inflammation is essential for establishing an accurate diagnosis and identifying etiology. Future research should emphasize the mechanism of inflammation resolution, immunometabolism, trained immunity, and tissue-specific immune regulation.

A deeper understanding of chronic inflammation will facilitate the development of targeted therapies capable of controlling pathological inflammation without compromising protective immunity and tissue repair.

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