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4.1 Introduction

Inflammation was described as early as 3000 BC in an Egyptian papyrus [1] and is still a common problem despite continuous advancements in prevention and treatment methods. The delineation of the site and extent of inflammation are crucial to the clinical management of infection and for monitoring the response to therapy [2].

This issue is relevant to nuclear medicine, since physiological along with morphological imaging has an important role in achieving this goal.

Inflammation is a complex tissue reaction to injury. Injury may be caused not only by living microbes, i.e., bacteria, viruses, or fungi, leading to infection, but also by injurious chemical, physical, immunological, or radiation agents:

- Physical agents
 - Trauma
 - Heat
- Chemical agents
 - Chemotherapy
 - Industrial accidents
- Immunological agents
 - Antigen-antibody reactions
- Radiation
 - Radiation therapy
 - Nontherapeutic radiation exposure

Inflammation is fundamentally a protective reaction against the cause of cell injury as well as the consequence of such injury. However, inflammation is potentially harmful and may even be life threatening. Since most of the essential

components of the inflammatory process are found in the circulation, inflammation occurs only in vascularized tissue. Inflammation is generally considered a nonspecific response, because it happens in the same way regardless of the stimulus and the number of exposures to the stimulus [2]. This is different from the immune system, which has memory, and the antigens are specific and induce a specific response.

4.2 Classification of Inflammation

Inflammation may be classified as acute or chronic. Acute inflammation is the immediate or early response to injury and is of relatively short duration. It lasts for minutes, hours, or at most a few days. Chronic inflammation, on the other hand, is of longer duration and may last from weeks to years [3]. The distinction between acute and chronic inflammation, however, depends not only on the duration of the process but also on other pathological and clinical features.

4.3 General Pathophysiological Changes of Inflammation

4.3.1 Local Pathophysiological Changes of Inflammation

4.3.1.1 Acute Inflammation

Acute inflammation continues only until the threat to the host has been eliminated, which usually takes 8–10 days, although this is variable. Inflammation is generally considered to be chronic when it persists for longer than 2 weeks [2]. Many regional and systemic changes accompany acute inflammation and are mediated by certain chemicals produced endogenously called chemical mediators and are behind the spread of the acute inflammatory response following injury to a small area of tissue into uninjured sites. These chemical mediators include mediators released from cells such as histamine and prostaglandins and others in plasma which are released by some systems contained in the plasma

which are the four enzymatic cascade systems: the complement, the kinins, the coagulation factors, and the fibrinolytic system which produce several inflammatory mediators [4–6]. Table 4.1 summarizes the main chemical mediators of inflammation.

Acute inflammation is characterized by the following major regional components:

Local Vascular Changes

1. Vasodilation following transient vasoconstriction is one of the most important changes that accompany acute inflammation, and it persists until the end of the process. It involves first the arterioles and then results in the opening of new capillary beds in the area.
2. Increased vascular permeability due to:
 - Contraction of endothelial cells with widening of intercellular gaps
 - Direct endothelial injury, resulting in endothelial cell necrosis and detachment
 - Leukocyte-mediated endothelial injury: Leukocytes adhere to the endothelium, which becomes activated, thereby releasing toxic oxygen species and proteolytic enzymes and causing endothelial injury.
 - Angiogenesis: With inflammation, endothelial cells may proliferate and form new capillaries and venular beds (angiogenesis). These capillary sprouts remain leaky until endothelial cells differentiate.
3. Stasis (slowing of circulation): Increased permeability with extravasation of fluid into the extravascular spaces results in concentration of red blood cells in the small vessels and increased viscosity of the blood, with slowing of circulation in the local vessels. Figures 4.1 and 4.2 illustrate the main vascular changes.

Formation of Exudate

Increased permeability of the microvasculature, along with the other changes described, leads to leakage with formation of “exudate,” an inflammatory extravascular fluid with a high protein content, much cellular debris, and a specific gravity above 1.020. This is the hallmark of acute inflammation, which may also be called exudative inflammation. It indicates significant alteration in

Table 4.1 Chemical mediators of inflammation

Mediator	Characteristics and role in inflammation
<i>A. Cell factors</i>	
Histamine	Stored in mast cells, basophil and eosinophil leukocytes, and platelets
Release from sites of storage is stimulated by complement components C3a and C5a and by lysosomal proteins released from neutrophils	
Responsible for vasodilation and the immediate phase of increased vascular permeability	
Lysosomal compound	Released from neutrophils and includes cationic proteins, which may increase vascular permeability, and neutral proteases, which may activate complement
Prostaglandins	Long-chain fatty acids derived from arachidonic acid and synthesized by many cell types. Some prostaglandins potentiate the increase in vascular permeability caused by other compounds
Leukotrienes	Synthesized from arachidonic acid, especially in neutrophils, and have vasoactive properties
5-Hydroxytryptamine (serotonin)	A potent vasoconstrictor present in high concentrations in mast cells and platelets
Lymphokines	Released by lymphocytes and may have vasoactive or chemotactic effects
<i>B. Plasma factors</i>	
Products of complement activation	
C5a	Chemotactic for neutrophils, increases vascular permeability, releases histamine from mast cells
C3a	Similar to but less active than C5a
C567	Chemotactic for neutrophils
C56789	Cytolytic activity
C4b, 2a, 3b	Facilitates phagocytosis of bacteria by macrophages (opsonization of bacteria)
Kinin system	Bradykinin included in the system is the most important vascular permeability factor, also a mediator for pain which is a major feature of acute inflammation
Coagulation factors	Responsible for the conversion of soluble fibrinogen into fibrin, a major component of the acute inflammatory exudate
Fibrinolytic system	Plasmin included in the fibrinolytic system is responsible for the lysis of fibrin into fibrin degradation products, which have a local effect on vascular permeability

the normal permeability of the small blood vessels in the region of injury.

The two components of exudate, fluid and protein, serve good purposes. Fluid increase helps to dilute the toxins. Protein increase includes globulins that provide protective antibodies, while fibrin helps to limit the spread of bacteria and promotes healing. Exudate varies in composition. In early or mild inflammation, it may be watery (serous exudate) with low plasma protein content and few leukocytes. In more

advanced inflammation, the exudate becomes thick and clotted (fibrinous exudate). When large numbers of leukocytes accumulate (Fig. 4.3), the exudate consists of pus and is called suppurative, while if it contains erythrocytes due to bleeding, it is referred to as hemorrhagic. Pus, accordingly, is a variant of exudate that is particularly rich in leukocytes, mostly neutrophils and parenchymal cell debris.

Exudate should be differentiated from “transudate,” which is a fluid with low protein

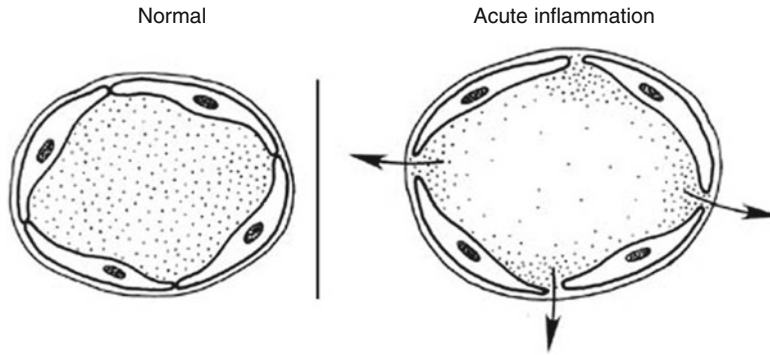


Fig. 4.1 Vasodilation of vessels and opening of the intercellular gaps in inflammation

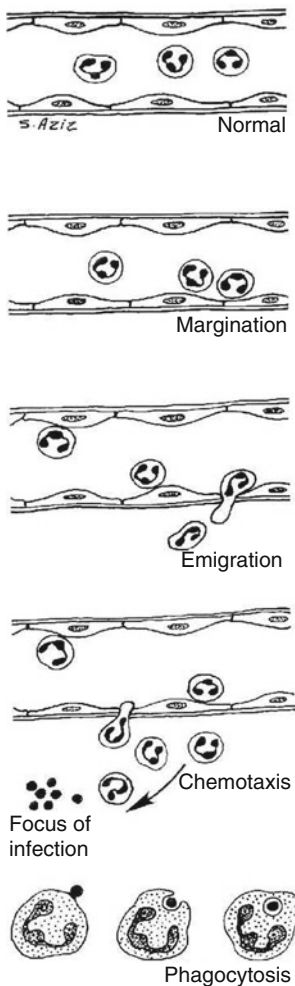


Fig. 4.2 Sequence of cellular changes that accompany inflammation

concentration and a specific gravity of less than 1.012. Transudation is associated with normal endothelial permeability [3, 5].

Local Cellular Events

1. Margination

After stasis develops, leukocytes will be peripherally oriented along the vascular endothelium, a process called leukocytic margination (Fig. 4.1).

2. Diapedesis (emigration)

Leukocytes emigrate from the microcirculation and accumulate at the site of injury.

3. Chemotaxis

Once outside the blood vessel, the cells migrate at varying rates of speed in interstitial tissue toward a chemotactic stimulus in the inflammatory focus. Through chemoreceptors at multiple locations on their plasma membranes, the cells are able to detect where the highest concentrations of chemotactic factors are and to migrate in their direction. Granulocytes, including the eosinophils, basophils, and some lymphocytes, respond to such stimuli and aggregate at the site of inflammation. The primary chemotactic factors include bacterial products, complement components C5a and C3a, kallikrein and plasminogen activators, products of fibrin degradation, prostaglandins, and fibrinopeptides. Histamine is not a chemotactic factor but facilitates the process. Some bacterial toxins,

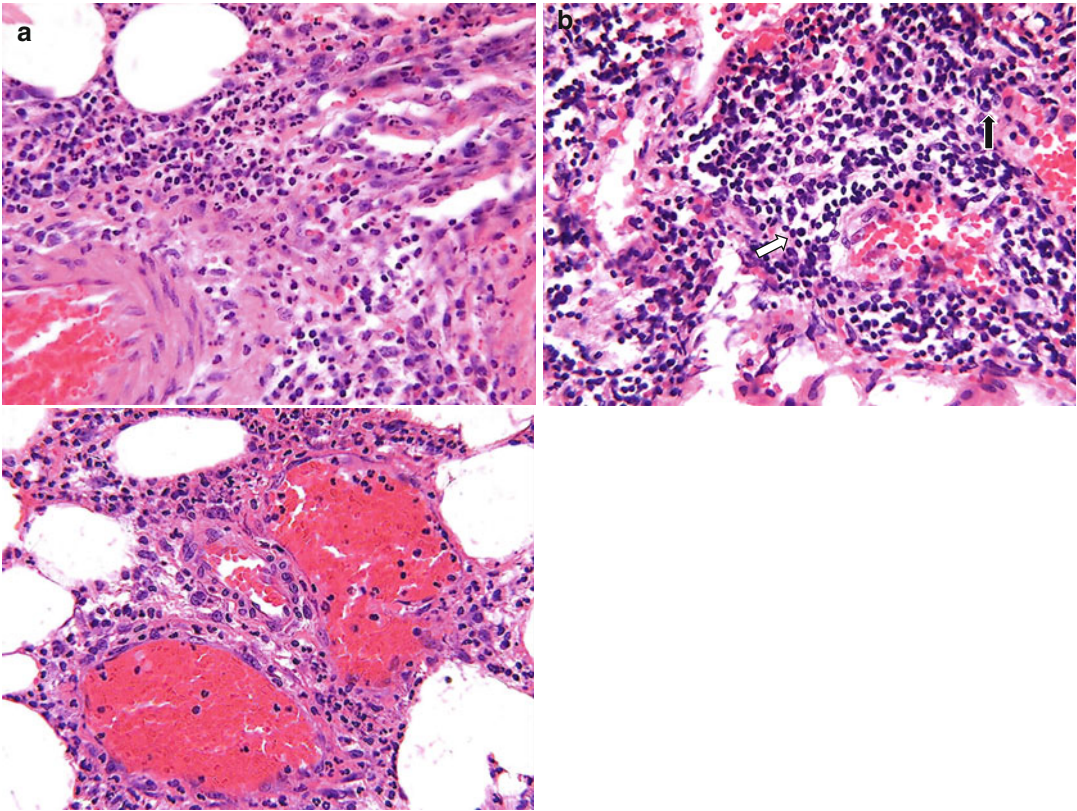


Fig. 4.3 (a) Microphotograph of acute inflammation showing numerous inflammatory cells particularly polymorphonuclear leukocytes, which are identified better (arrows) on higher power. (b) Microphotograph of

chronic inflammation illustrating the different types of inflammatory cells, the mononuclear cells including lymphocytes (arrow) and plasma cells (open arrow)

particularly from gram-negative bacteria and streptococcal streptolysins, inhibit neutrophil chemotaxis [2, 3, 5].

4. Phagocytosis

This defense mechanism is particularly important in bacterial infections. The polymorphonuclear leukocytes and macrophages ingest debris and foreign particles.

4.3.1.2 Local Sequelae of Acute Inflammation

Acute inflammation has several possible local sequelae. These include resolution, suppuration (formation of pus), organization, and progression to chronic inflammation. Resolution means complete restoration of tissues to normal. Organization of tissues refers to their replacement by granula-

tion tissue with formation of large amounts of fibrin, growth of new capillaries into fibrin, migration of macrophages into the zone, and proliferation of fibroblasts resulting in fibrosis and consequently exudate becoming organized.

4.3.1.3 Chronic Inflammation

Acute inflammation may progress to a chronic form characterized by reduction of the number of polymorphonuclear leukocytes but proliferation of fibroblasts with collagen production. Commonly, chronic inflammation may be primary with no preceding acute inflammatory reaction. Chronic inflammation, whether following acute inflammation or not, is characterized by a proliferative (fibroblastic) rather than an exudative response with predominantly mononuclear

cell infiltration (macrophages, lymphocytes, and plasma cells) (Fig. 4.3b). Vascular permeability is also abnormal, but to a lesser extent than in acute inflammation with formation of new capillaries.

4.3.1.4 Abscess Formation

Abscess is defined as a collection of pus in tissues, organs, or confined spaces, usually caused by bacterial infection. The first phase of abscess formation is cellulitis, characterized by hyperemia, leukocytosis, and edema, without cellular necrosis or suppuration. This stage is also called phlegmon. It may be followed in some organisms by necrosis and liquefaction and walling off of the pus, which results in abscess formation that can be present with both acute and chronic inflammation.

4.3.2 Systemic Pathophysiological Changes of Inflammation

Three major systemic changes are associated with inflammation: leukocytosis, fever, and an increase in plasma proteins. Leukocytosis is an increased production of leukocytes due to stimulation by several products of inflammation such as complement component C3a and colony-stimulating factors. A febrile response is due to the pyrogens. The increase in plasma proteins is due to the stimulation of the liver by some products of inflammation, leading to increased synthesis of certain proteins referred to as acute-phase reactants which include C-reactive protein, fibrinogen, and haptoglobin and are anti-inflammatory [2].

4.3.3 Pathophysiological Changes of Healing

Healing of tissue after injury is closely linked to inflammation since it starts by acute inflammation. Healing may lead to restoration of normal structure and function of the injured tissue (resolution) or to the formation of a scar consisting of collagen (repair) when resolution cannot be achieved because the tissue is severely injured or cannot regenerate.

In either case, acute inflammation occurs first and for this reason is considered the defensive

phase of healing. Healing (resolution and repair) occurs in two overlapping phases, reconstruction and maturation, and may take as long as 2 years. The reconstructive phase starts 3–4 days after injury, continues for approximately 2 weeks, and is characterized by fibroblasts followed by collagen synthesis. The maturation phase is characterized by cell differentiation, scar formation, and remodeling of the scar; it begins several weeks after injury and may take up to 2 years to complete.

4.4 Pathophysiology of Major Soft Tissue Inflammation

4.4.1 Abdominal Inflammation

An abdominal abscess may be formed in an abdominal organ or within the abdomen outside the organs. There are several types of abdominal infection: abscess; cellulitis (phlegmon), i.e., early inflammation of the soft tissue prior to or without formation of an abscess; and peritonitis. Abscesses fall into three categories:

1. Intraperitoneal abscess
 - Subphrenic
 - Midabdominal
 - Right lower quadrant
 - Left lower quadrant
 - Pelvic abscess
2. Retroperitoneal abscess
 - Anterior retroperitoneal
 - Perinephric
3. Visceral abscess
 - Hepatic
 - Pancreatic
 - Splenic

The organisms causing abscesses may reach the tissue by direct implantation such as penetrating trauma, may spread from contiguous infection, through hematogenous or lymphatic routes from a distant site, or through migration of resistant flora into an adjacent, normally sterile area such as in perforation of an abdominal viscus.

Factors predisposing to abscess formation include impaired host defense mechanisms; trauma/surgery; obstruction of urinary, biliary, or respiratory passages; foreign bodies; chemical or immunological irritation; and ischemia. Abdominal surgery (particularly of the colon,

appendix, and biliary tree) and trauma are the most common; less common are appendicitis, diverticulitis, and pelvic inflammatory disease. The formation of fibrin in the abdominal cavity is a common pathophysiological pathway for abdominal abscess formation due to diminished fibrin degradation. Hyaluronan-based agents were found to reduce adhesion formation after surgery and reduce abscess formation in experimental peritonitis. Possible mechanisms of action of hyaluronan include modulation of the inflammatory response and enhanced fibrinolysis [7]. Low pH, large bacterial inocula, poor perfusion, the presence of hemoglobin, and large amounts of fibrin (which impedes antibiotic penetration) make the abscess a cloistered environment that is penetrated poorly by many antimicrobial therapies [8, 9]. Therefore, management of these infections requires prompt recognition, early localization, and effective drainage, as well as appropriate antimicrobial use. Once the diagnosis is made and the abscess is localized, treatment should begin promptly. Percutaneous or open surgical drainage should be used. Broad-spectrum antibiotics should be given until culture and sensitivity data are obtained. Localization is crucial since, for example, percutaneous drainage is inappropriate for abscesses in certain locations such as the posterior subphrenic space or in the porta hepatis. In the liver, abscesses occur in the right lobe in approximately 95 % of the cases, and in 70 % of cases, the liver abscesses are solitary [10].

Accumulation of leukocytes in the abscess is the pathophysiological basis for using labeled white blood cells for abscess imaging. In the acute phase, migration of leukocytes is vigorous. Later, the migration rate slows, and the cell type changes from predominantly neutrophils to mononuclear cells (lymphocytes, plasma cells, and macrophages). This pathophysiological change associated with the chronic state explains the better diagnostic accuracy of labeled leukocyte scans in acute as opposed to chronic abscesses.

Inflammatory bowel disease (IBD) is an idiopathic disease, probably involving an immune reaction of the body to its own intestinal tract. The two major types of IBD are ulcerative colitis (UC) and Crohn's disease (CD). Crohn's disease is also referred to as regional enteritis, terminal ileitis, or granulomatous ileocolitis. IBD is a dis-

ease of industrialized nations and observed most commonly in Northern Europe and North America. Incidence among whites is approximately four times that of other races, slightly greater in females and higher in Ashkenazi Jews (those who have immigrated from Northern Europe) than in other groups. The risk of developing UC is higher in nonsmokers and former smokers than in current smokers. Incidence peaks in the second and third decades of life. A second smaller peak occurs in patients aged 55–65 years. CD and UC can occur in childhood, although the incidence is much lower in children younger than 15 years with some differences in presentation and more negative effect on quality of life in younger age group [11].

The etiology of IBD is unsettled. Suspected factors include environmental, infectious, genetic, autoimmune, and host factors. A great deal of research has been performed to discover potential genes linked to IBD. One of the early linkages discovered was on chromosome 16 (*IBD1* gene), which led to the identification of the *NOD2* gene (now called *CARD15*) as the first gene clearly associated with IBD (as a susceptibility gene for Crohn's disease). Studies have also provided strong support for IBD susceptibility genes on chromosomes 5 (5q31) and 6 (6p21 and 19p). None of these mechanisms have been implicated as the primary cause, but they are postulated as potential causes. The lymphocyte population in persons with IBD is polyclonal, making the search for a single precipitating cause difficult. The trigger for the activation of the immune response has not been defined. However, possible triggers include a pathogenic organism (unidentified yet), an immune response to an intraluminal antigen (e.g., cow's milk protein), or an autoimmune process with immune response to an intraluminal antigen and a similar antigen present on intestinal epithelial cells. In any case, activation of the immune system leads to inflammation of the intestinal tract, both acute and chronic [12–19].

The pathophysiology of IBD is still incompletely understood and is under active investigation, but the common end pathway is inflammation of the mucosal lining of the intestinal tract, causing ulceration, edema, bleeding, and fluid and electrolyte loss. The inflammation of the intestinal mucosa includes both acute inflammation

with neutrophilic infiltration and chronic with mononuclear cell infiltration (lymphocytic and histiocytic) [20].

In UC, inflammation always begins in the rectum, extends proximally a certain distance, and then abruptly stops. A clear demarcation exists between involved and uninvolved mucosa. The rectum is always involved in UC, and no “skip areas” are present. UC primarily involves the mucosa and the submucosa, with formation of crypt abscesses and mucosal ulceration. The mucosa typically appears granular and friable. In more severe cases, pseudopolyps form, consisting of areas of hyperplastic growth with swollen mucosa surrounded by inflamed mucosa with shallow ulcers. In severe UC, inflammation and necrosis can in rare cases extend below the lamina propria to involve the submucosa and the circular and longitudinal muscles.

UC remains confined to the rectum in approximately 25 % of cases. In the remainder of cases, UC spreads proximally and contiguously. Pancolitis occurs in 10 % of patients. The small intestine is essentially not involved, except when the distal terminal ileum is inflamed in a superficial manner, referred to as backwash ileitis. Even with less than total colonic involvement, the disease is strikingly and uniformly continuous. As the disease becomes chronic, the colon becomes a rigid foreshortened tube that lacks its usual haustral markings, leading to the lead pipe appearance observed on barium enema. The skip areas (normal areas of the bowel interspersed with diseased areas) observed in CD of the colon do not occur in UC.

CD, on the other hand, consists of segmental involvement by a nonspecific granulomatous inflammatory process. The most important pathological feature is the involvement of all layers of the bowel, not just the mucosa and the submucosa, as is characteristic of UC.

Furthermore, CD is discontinuous, with skip areas interspersed between one or more involved areas. Late in the disease, the mucosa develops a cobblestone appearance, which results from deep longitudinal ulcerations interlaced with intervening normal mucosa. The three major patterns of involvement in CD are (1) disease in the ileum and cecum, occurring in 40 % of patients; (2) disease confined to the small intestine, occurring in 30 % of patients; and (3) disease confined to the colon, occurring in 25 % of patients. Rectal spar-

ing is a typical but not constant feature of CD. However, anorectal complications (e.g., fistulas, abscesses) are common. Much less commonly, CD involves the more proximal parts of the GI tract, including the mouth, tongue, esophagus, stomach, and duodenum. CD causes three patterns of involvement: (1) inflammatory disease, (2) strictures, and (3) fistulas.

The incidence of gallstones and kidney stones is increased in CD because of malabsorption of fat and bile salts. Gallstones are formed because of increased cholesterol concentration in the bile, caused by a reduced bile salt pool. Patients who have CD with ileal disease or resection also are likely to form calcium oxalate kidney stones. With the fat malabsorption, unabsorbed long-chain fatty acids bind calcium in the lumen. Oxalate in the lumen normally is bound to calcium. Calcium oxalate is poorly soluble and poorly absorbed; however, if calcium is bound to malabsorbed fatty acids, oxalate combines with sodium to form sodium oxalate, which is soluble and is absorbed in the colon (enteric hyperoxaluria). The development of calcium oxalate stones in CD requires an intact colon to absorb oxalate. Patients with ileostomies do not develop calcium oxalate stones. Extraintestinal manifestations of IBD include iritis, episcleritis, arthritis, and skin involvement, as well as pericholangitis and sclerosing cholangitis.

The most common causes of death in IBD are peritonitis with sepsis, malignancy, thromboembolic disease, and complications of surgery. Malnutrition and chronic anemia are observed in long-standing CD. Children with CD or UC can exhibit growth retardation.

Patients with UC most commonly present with bloody diarrhea, whereas patients with CD usually present with non-bloody diarrhea. Abdominal pain and cramping, fever, and weight loss occur in more severe cases. The presentation of CD is generally more insidious than that of UC. UC and CD are generally diagnosed using clinical, endoscopic, and histologic criteria. However, no single finding is absolutely diagnostic for one disease or the other. Furthermore, approximately 20 % of patients have a clinical picture that falls between CD and UC; they are said to have indeterminate colitis. Accordingly, imaging may be needed for the detection and for evaluation of the disease activity during its course.

4.4.2 Chest Inflammation

The chest is a common site of various types of infection, acute and chronic. Such infections are frequent in the elderly and in immunosuppressed patients, including cancer patients. Common inflammatory conditions relevant to nuclear medicine include pneumonia, sarcoidosis, diffuse interstitial fibrosis, and *Pneumocystis (jiroveci) carinii* pneumonia (See also Chap. 12).

4.4.2.1 Sarcoidosis

Sarcoidosis is an inflammatory condition of uncertain etiology characterized by the presence of noncaseating granulomas involving multiple organs. The disease is now recognized as a member of a large family of granulomatous disorders and has been reported from all parts of the world. Current evidence points to genetic predisposition and exposure to yet unknown transmissible agent(s) and/or environmental factors as etiological agents [21]. The lung is most commonly and usually the first site of involvement, and the inflammatory processes extend through the lymphatics to the hilar and mediastinal nodes [22]. The lung is involved in more than 90 % of cases. Pulmonary sarcoidosis starts as diffuse interstitial alveolitis, followed by the characteristic granulomas. Granulomas are present in the alveolar septa as well as in the walls of the bronchi and pulmonary arteries and veins. The center of the granuloma contains epithelioid cells derived from mononuclear phagocytes, multinucleated giant cells, and macrophages. Lymphocytes, macrophages, monocytes, and fibroblasts are present at the periphery of the granuloma [23]. Sarcoidosis represents a challenge to clinical investigation because of its unpredictable course, uncertain response to therapy, and diversity of potential organ involvement and clinical presentations [24]. The diagnosis is based on a compatible clinical and/or radiological picture, histopathological evidence of noncaseating granulomas in tissue biopsy specimens, and exclusion of other diseases capable of producing similar clinical or histopathological appearances. Even microscopically, the noncaseating granulomas are not specific [21]. Infection by mycobacterial species other than *Mycobacterium tuberculosis* frequently leads to the production of noncaseating granulomas [25]. The condition is underdiagnosed

in some areas. However, owing to the increasing awareness, it is being diagnosed more frequently than a few decades ago [26].

The disease runs a benign course with spontaneous remission of the activity though some degree of residual pulmonary function abnormality persists. Only a minority of patients develop complicated disease that may lead to blindness, renal failure, liver failure, and heart involvement.

Corticosteroids remain the mainstay of treatment. Treatment under close clinical monitoring should be tailored to suit the needs of the individual patient hence the need to evaluate disease activity [26].

Advanced age, the presence of pulmonary symptoms, the presence of parenchymal lesions on chest radiograph, a previous history of treatment with corticosteroids, and the presence of extrathoracic involvements at the time of detection are possible prognostic factors in patients with sarcoidosis [27]. The mode of onset and the extent of the disease are also related to prognosis. An acute onset with erythema nodosum or asymptomatic bilateral hilar lymphadenopathy usually heralds a self-limiting course, whereas an insidious onset, especially with multiple extrathoracic lesions, may be followed by relentless, progressive fibrosis of the lungs and other organs

4.4.2.2 *Pneumocystis carinii* (jiroveci) Pneumonia

Pneumocystis carinii (jiroveci) pneumonia (PCP) is a condition that may be endemic or epidemic. It is caused by *Pneumocystis carinii*, which was considered as a protozoon and recently as a fungus. The condition is common in premature infants, debilitated children, and in other immunocompromised conditions, particularly the acquired immune deficiency syndrome (AIDS), but it is also seen in congenital immunodeficiency and in patients who are receiving chemotherapy and corticosteroids. It remains a significant cause of morbidity and mortality in human immunodeficiency virus and nonhuman immunodeficiency virus-associated immunosuppressed patients [28]. It is the most common infection in AIDS patients, and it remains an important cause of morbidity and mortality [29]. The introduction of highly active antiretroviral therapy in industrialized nations however has led

to dramatic declines in the incidence of AIDS-associated complications, including PCP. In the developing countries, no decline has occurred [30]. Transmission is usually airborne. The pathological changes are predominantly in the lungs with an inflammatory reaction consisting of plasma cells of variable amount, monocytes, and histiocytes. This disease has also been reported in immunocompetent patients, and in this case the presentation is more closely resembling the disease of immunocompromised patients other than AIDS patients [31, 32]. The diagnosis is currently established through identification of the organisms in bronchial secretions obtained by bronchoalveolar lavage or bronchial washings [33]. Gallium-67 is an important imaging modality that helps in the diagnosis and evaluation of the activity of the disease.

4.4.2.3 Interstitial Pulmonary Fibrosis

Interstitial pulmonary fibrosis, a sometimes fatal condition, is characterized by parenchymal inflammation and interstitial fibrosis. The pathological changes start with alveolitis; this is followed by derangement of the alveolar-capillary units, leading to the end stage of fibrosis. There is a correlation between the inflammatory activity and the amount of gallium-67 activity in the lungs [34].

4.4.3 Renal Inflammation

Urinary tract infection (UTI) is common particularly in children. There are two main varieties of acute renal infection: pyelitis, which is confined to the renal pelvis, and pyelonephritis, where the renal parenchyma is also involved. It is not always possible to differentiate between the two conditions on clinical grounds. The pathology of acute pyelitis is not very well understood. The importance of the condition, however, lies in the fact that recurrent subclinical attacks are believed to be significant in the pathogenesis of chronic pyelonephritis [35].

The number of patients with chronic kidney disease and consequent end-stage renal disease is rising worldwide [36]. End-stage kidney disease,

defined as that requiring dialysis or receipt of a transplant or that which may lead to death from chronic kidney failure, generally affects less than 1 % of the population [37]. Among today's challenges is to identify those at greatest risk for end-stage renal disease and intervene effectively to prevent progression of early chronic kidney disease and conditions leading to chronic disease [37].

Rarely, uncomplicated acute pyelonephritis causes suppuration and renal scarring. However, urinary infections in patients with renal calculi, obstructed urinary tract, neurogenic bladder, or diabetes are frequently much more destructive and have ongoing sequelae [38].

4.4.3.1 Acute Pyelonephritis

Acute pyelonephritis is a common medical problem. The diagnosis and management of this condition is complex. Patients initially diagnosed with pyelonephritis typically exhibit symptoms and laboratory evidence suggesting infected urine, with signs referable to upper urinary tract infection. However, no consistent set of signs and symptoms are sensitive and specific for this diagnosis. Symptoms of acute pyelonephritis generally develop rapidly over a few hours or a day. Symptoms of lower UTI may or may not be present. These include dysuria; urinary frequency, hesitancy, and urgency; gross hematuria; and suprapubic discomfort, heaviness, pain, or pressure. Additionally, flank pain and tenderness, unilateral or sometimes bilateral, are present. Fever is not always present. When present, it is not unusual for the temperature to exceed 103 °F (39.4 °C). Rigor, chills, malaise, and weakness may be present. Anorexia, nausea, vomiting, and diarrhea may also be present. Most patients have significant leukocytosis, pyuria with leukocyte casts in the urine, and bacteria on a gram stain of unspun urine.

Many conditions and clinical situations are associated with an increased risk of pyelonephritis. Table 4.2 lists common risk factors.

Pyelonephritis is significantly more common in females (higher in white than in black) compared to males. Approximately 10–30 % of women develop a symptomatic UTI at some point in their lives.

Table 4.2 Common risk factors for pyelonephritis

Mechanical factors
Obstruction
Prostatic infection
Calculi
Urinary diversion procedure
Infected cysts
External drainage with urinary catheters or nephrostomy tubes
Stents
Vesicoureteral reflux
Neurogenic bladder
Bladder or renal abscesses
Fistulas
Recent urinary tract instrumentation
Metabolic and hormonal factors
Diabetes mellitus
Pregnancy
Renal impairment
Malakoplakia
Primary biliary cirrhosis
Immune factors
Transplant recipients
Neutropenia
Congenital or acquired immunodeficiency syndromes
Infectious factors (unusual pathogens)
Yeasts and fungi
<i>Mycoplasma</i> species
Resistant bacteria, including <i>P. aeruginosa</i>
Calculi-predisposing bacteria, including <i>Proteus</i> species and <i>Corynebacterium urealyticum</i>
Other factors
Uncircumcised penis
Old age
Recent antimicrobial use

Adapted from [39, 40]

Acute pyelonephritis is a bacterial infection of the kidney with acute inflammation of the pyelocaliceal lining and renal parenchyma centrifugally along medullary rays. This can occur by more than one way. Most often it occurs because of ascending infection from the lower urinary tract (Fig. 4.4). The initial colonization of the walls of the ureter is in areas of turbulent flow which leads to paralysis of peristalsis. Dilation and functional obstruction result in subsequent pyelonephritis. Another way is by direct reflux of bacteria. Hematogenous spread to the kidney by

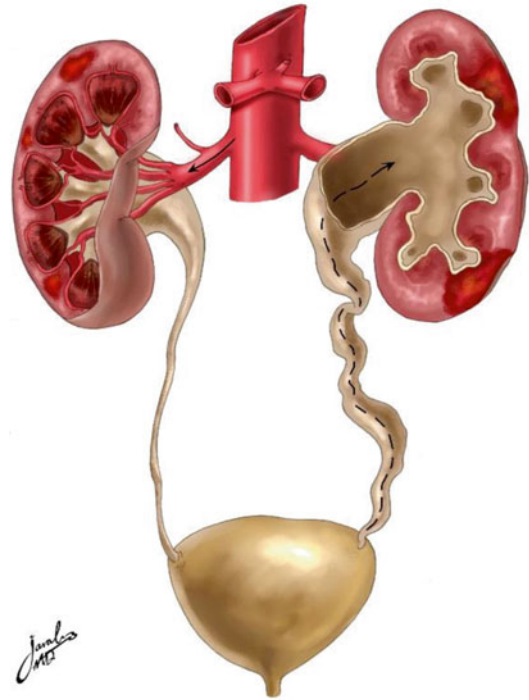


Fig. 4.4 Diagram illustrating the routes of inducing urinary tract infection. The left-hand side represents the hematogenous route, while the right-hand side represents the retrograde route such as with vesicoureteral reflux

gram-positive and less likely by gram-negative organisms is the third way that can occur. This has become less prevalent since the advent of rapid use of antibiotics. Little or no evidence supports lymphatic spread.

Grossly, the kidney is enlarged and edematous. The cut surface may show small abscesses in the cortex, and more often there are wedge-shaped purulent areas streaking upward from the medulla, with normal areas of the kidney tissue intervening in between infected zones (Fig. 4.5). Frequently, the pelvis and calyces are inflamed and dilated. In severe infection, renal papillary necrosis may be present.

Microscopically, there is intense inflammation, with infiltration of polymorphonuclear leukocytes throughout the interstitial tissue and abscess formation. There is destruction of the tubules, but the glomeruli and blood vessels are often unaffected. The disease remains essentially focal in character, with areas of normal tissue. Following treatment and

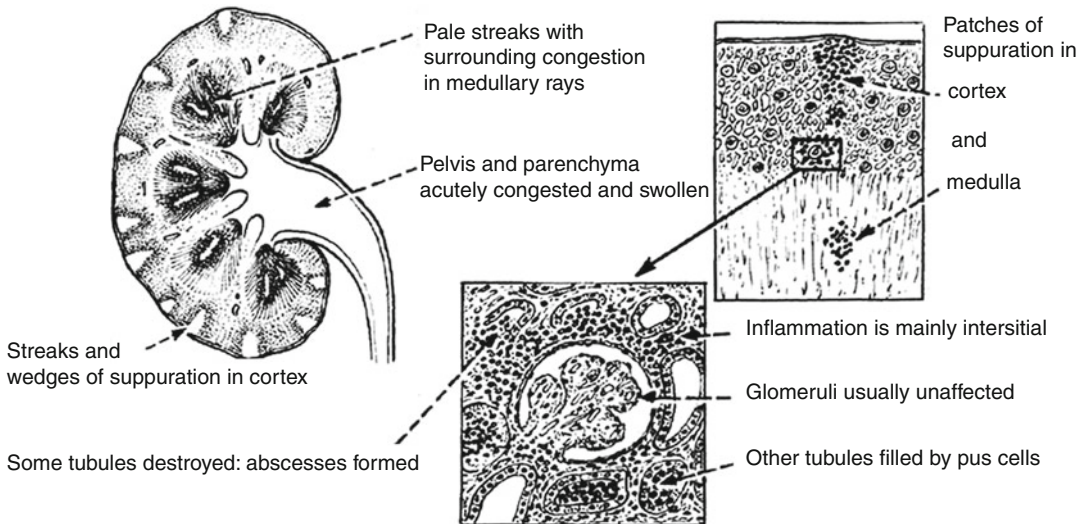


Fig. 4.5 Acute pyelonephritic changes (Modified from [41] with permission)

removal of predisposing factors such as obstruction, healing may occur, leaving coarse scars which stretch from the medulla to the capsule of the kidney.

4.4.3.2 Chronic Pyelonephritis

Chronic pyelonephritis is a chronic condition affecting the pelvis and parenchyma and resulting from recurrent or persistent renal infection. It occurs almost exclusively in patients with major anatomic anomalies, including urinary tract obstruction, struvite calculi, renal dysplasia, or, most commonly, vesicoureteral reflux (VUR) in young children. Grossly, the kidney shows normal areas alternating with zones of scarring. Wedge-shaped scars can be seen on the subcapsular surface of the kidney. The appearance differs, depending on the presence or absence of obstruction. Chronic pyelonephritis in the presence of intra- or extrarenal obstruction shows dilation of the pelvocalyceal system and sometimes peripelvic fibrosis. If no obstruction is present, the pelvic change is in the form of peripelvic fibrosis rather than dilation (Fig. 4.6).

Microscopically, the scarred areas show changes in the interstitium and tubules. The interstitial tissue shows infiltration by predominantly lymphocytes and plasma cells.

The tubules become atrophic and may collapse (Fig. 4.7). The glomeruli may be normal in some cases, while in others periglomerular fibrosis is present.

4.5 Pathophysiology of Major Skeletal Inflammations

Osteomyelitis indicates an infection involving the cortical bone as well as the marrow (see Chap. 6). It is classified into many types based on several pathological and clinical factors [42–49] including route of infection, patient age, etiology, and onset. Hematogenous osteomyelitis most commonly affects children, and the metaphyses of long bones are the most common sites. Nonhematogenous osteomyelitis, on the other hand, occurs as a result of penetrating trauma, spread of a contiguous soft tissue infection, or inoculation, as in drug addicts [48–54]. Many organisms have been encountered in the pathogenesis of osteomyelitis, particularly gram-positive organisms, the most common being *Staphylococcus aureus* [44–46]. Like many other pathological conditions of bone, infections cause reactive new bone formation which – among other factors, particularly increased blood flow – is the principle reason for the accumulation of

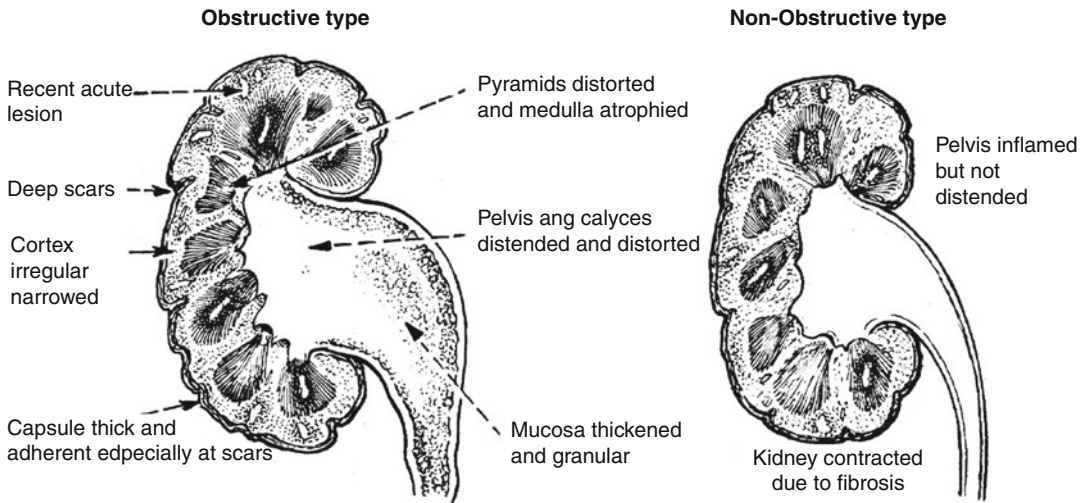


Fig. 4.6 Types of pyelonephritic changes based on whether obstruction is present (From [41] with permission)

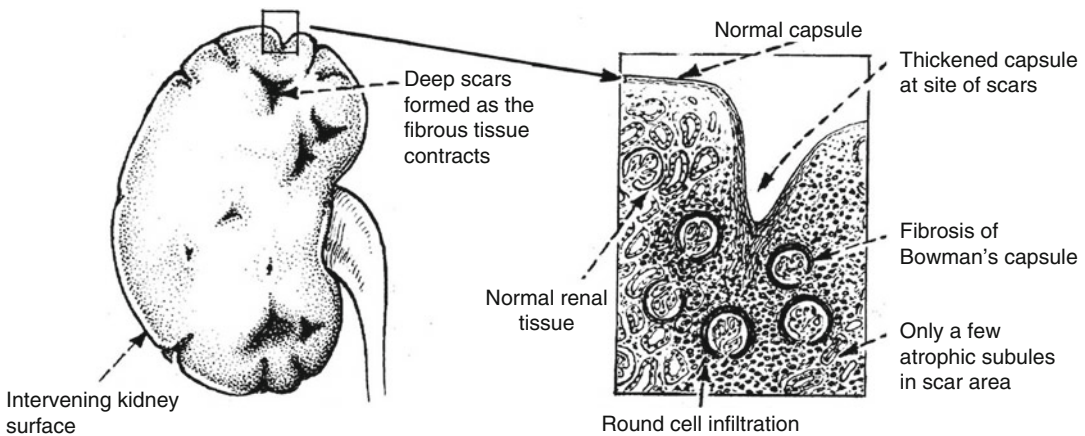


Fig. 4.7 Main pathological changes of chronic pyelonephritis (From [41] with permission)

bone-seeking radiopharmaceuticals at the site of skeletal infections.

It is difficult to draw the line between acute and chronic osteomyelitis. Chronic osteomyelitis has been defined as a skeletal infection with a duration as short as 5 days or as long as 6 weeks. It is characterized by less marked inflammatory cell infiltrates than acute infection and may exhibit a variable amount of necrotic tissue. Acute septic arthritis is a medical emergency, since it may result in destruction of the articular cartilage and permanent disability if treatment is

delayed [55]. See Chap. 6 for more details on skeletal inflammations.

4.6 Fever of Unknown Origin

FUO describes an illness of several episodes of fever exceeding 38.3°C or at least 3-week duration, with no diagnosis after an appropriate inpatient or outpatient evaluation. There are many causes of fever of unknown origin. Infection accounts for only about 25 % of these causes.

Neoplasms are responsible for approximately 15–25 %. Other etiologies include collagen vascular disease, granulomatous diseases, pulmonary emboli, cerebrovascular accidents, and drug fever [56].

4.7 Radiopharmaceuticals for Inflammation Imaging

Many radioisotopes have been used to detect and localize infection (see Table 4.3). Several mechanisms explain the uptake of these radiotracers at the site of infection:

1. Increased vascular permeability
 - ^{111}In and $^{99\text{m}}\text{Tc}$ human polyclonal IgG
 - ^{111}In monoclonal IgM antibody
 - ^{111}In and $^{99\text{m}}\text{Tc}$ liposomes
 - ^{111}In biotin and streptavidin
 - $^{99\text{m}}\text{Tc}$ nanocolloids
 - ^{111}In chloride
 - ^{67}Ga citrate
2. Migration of WBCs to the site of infection
 - ^{111}In - and $^{99\text{m}}\text{Tc}$ -labeled leukocytes
 - $^{99\text{m}}\text{Tc}$ anti-WBC antibodies
3. Binding to proteins at the site of infection, i.e., ^{67}Ga citrate (lactoferrin and other iron-containing proteins)
4. Binding to WBCs at the site of infection
 - Chemotactic peptides
 - Interleukins
5. Binding to bacteria
 - $^{99\text{m}}\text{Tc}$ -labeled ciprofloxacin antibiotic
 - ^{67}Ga citrate
6. Metabolic trapping, i.e., F-18 fluorodeoxyglucose

Since there are limitations to the radiopharmaceuticals available for imaging infection, the search continues for better agents with ideal properties [56–59]. They should:

 1. Be easy to prepare
 2. Have low cost and wide availability
 3. Ensure rapid detection and localization of infections (< 3 h)
 4. Have low toxicity and produce no immune response
 5. Clear rapidly from the blood with no significant uptake in the liver, spleen, GI tract, bone, kidneys, bone marrow, or muscle

Table 4.3 Radiopharmaceuticals for imaging infection [56–58]

Gallium-67 citrate
Labeled WBCs using ^{111}In -oxine or $^{99\text{m}}\text{Tc}$ -HMPAO ($^{99\text{m}}\text{Tc}$ -hexamethylpropyleneamine oxime)
Labeled particles
Nanocolloid
Liposomes
Labeled large protein
Nonspecific immunoglobulins
Specific immunoglobulins: polyclonal and monoclonal
Antigranulocyte monoclonal antibodies
Anti-E-selectin antibodies
Labeled receptor-specific small proteins and peptides
Chemotactic peptides
Interleukins
Labeled antibiotics: ciprofloxacin
^{18}F -FDG

6. Clear rapidly from the background
7. Have high specificity and sensitivity and be able to differentiate infection from other causes of inflammation and tumors
8. Be able to differentiate acute from chronic infection

Gallium-67 has been used for many years to detect inflammation. The multiple mechanisms of uptake of gallium by inflammatory tissue include the following:

1. Increased vascular permeability
2. Gallium-67-binding substances at the site of inflammation
 - Transferrin (due to leakage of plasma proteins)
 - Lactoferrin (secreted with lysosomal contents of stimulated or dead neutrophils)
 - Siderophores produced by bacteria
3. Leukocytes: direct uptake
4. Bacteria: direct uptake

Sfakianakis et al. [60] found that ^{111}In leukocyte imaging accuracy was best for relatively acute infections (less than 2 weeks) but yielded a 27 % false-negative rate among patients with prolonged infections. On the other hand, ^{67}Ga imaging had its highest sensitivity in long-standing processes, with false-negative results of 19 % in relatively acute infections of less than 1-week

duration. In a comparative study of rabbits with experimental abscesses, Bitar et al. [61] found that ^{111}In leukocytes were clearly superior to gallium for imaging early abscesses. Furthermore, they found that the accumulation of ^{111}In leukocytes in experimental subcutaneous abscesses was inversely proportional to the age of the abscess. In abscesses 1–2 h, 6–8 h, 24 h, and 7 days old, 10.4, 5.2, 3, and 0.73 % of the injected dose, respectively, was accumulated. ^{67}Ga uptake, on the other hand, was not significantly affected by abscess age (Table 4.4). In abscesses 7 days old, ^{67}Ga accumulated to a greater extent than did ^{111}In -labeled leukocytes. Thus, Bitar et al., based on animal studies, and Stakianakis et al. came independently to the conclusion that ^{111}In -labeled WBCs are more suitable for acute infections of short duration, while ^{67}Ga labeling is better for infections of longer duration.

In rats, McAfee et al. [62] showed that as many as 10 % of circulating neutrophils accumulate daily at focal sites of inflammation. This high propensity of white blood cells to migrate to an abscess makes positive identification of the abscess likely on an ^{111}In WBC image. The authors also showed abscess-to-muscle ratios of

3,000 to 1 with ^{111}In WBCs at 24 h compared with 72 to 1 with ^{67}Ga and 7 to 1 with ^{111}In chloride. Accordingly, a small dose of only 500 μCi of ^{111}In leukocytes is sufficient for positive identification and localization of abscesses on an image. In ^{67}Ga imaging, a higher dose of approximately 5 mCi is needed. There is a higher radiation dose to the spleen from 500 μCi of ^{111}In WBC but radiation doses to gonads, marrow, and the whole body are higher with 5 mCi of ^{67}Ga . $^{99\text{m}}\text{Tc}$ HMPAO-labeled WBCs could provide fast diagnosis and localization of the abdomen (within 2–4 h). Physiological bowel activity, however, is found in 7 % at 2 h and in 28 % of patients imaged with this agent at 4 h. Leukocytes labeled with ^{111}In or $^{99\text{m}}\text{Tc}$ HMPAO are superior to those labeled with ^{67}Ga for acute infections in terms of sensitivity and specificity [63, 64].

In a recent systematic review of the published studies in humans cited in PubMed written in English, French, German, Italian, and Spanish, it was again found that labeled leukocyte is a sensitive method to localize abdominal abscesses and can guide dedicated US and CT investigations to improve their diagnostic potential [65].

Table 4.5 lists the main advantages and disadvantages of the major radiopharmaceuticals used for inflammation imaging.

Several monoclonal antibodies are used to detect infections. These antibodies are mainly directed against receptors on inflammatory cells.

Labeled antigranulocyte agents most commonly used are intact murine immunoglobulin G (IgG) antibodies against normal cross-reactive antigen-95 (anti-NCA-95, $^{99\text{m}}\text{Tc}$ -BW250/183, $^{99\text{m}}\text{Tc}$ -besilesomab [Scintimun®]) and the murine

Table 4.4 Comparison of uptake of ^{111}In WBC and ^{67}Ga citrate in experimental abscesses of varying age

Abscess age	Percent uptake ^{111}In WBC	^{67}Ga citrate
1–2 h	10.4	1.5
6–8 h	5.2	1.5
24 h	3	1.4
7 days	0.73	1.1

From [61]

Table 4.5 Advantages and disadvantages of the main available radiopharmaceuticals for inflammation

	Gallium-67 citrate	^{111}In WBC	$^{99\text{m}}\text{Tc}$ -HMPAO WBC
Advantages	Whole-body imaging	Whole-body imaging	Whole-body imaging
		Highly specific for infection	Earlier diagnosis (2–4 h)
			Better physical characteristics of technetium than ^{67}Ga and ^{111}In
Disadvantages	Results after 24 h or more	Tedious procedure	Tedious procedure
	Physiological liver, spleen, and bowel activity	Results at 24 h	Physiological bowel activity by 2 h
	Uptake in tumors	Physiological liver and spleen activity	Normal urinary activity

Fab fragment of the IgG antibody directed against the glycoprotein cross-reactive antigen-90 (anti-NCA-90, ^{99m}Tc -sulesomab, LeukoScan®). The ^{99m}Tc anti-NCA-90 Fab fragments can recognize a specific cross-reacting antigen (NCA-90) (the surface antigenic glycoprotein) on granulocytes, promyelocytes, and myelocytes [66–68]. LeukoScan uptake at the site of infection is explained partly by the migration of circulating antibody-labeled granulocytes to the site of infection. Uptake is also explained by the fact that the greater proportion of the labeled antibody fragment is in a free soluble form which can easily cross capillary membranes, binding to the leukocyte once in situ. This mechanism is favored by the increased capillary permeability at the site of infection. An important advantage of LeukoScan is the 5 min preparation time compared with the 2 h 30 min required by a specialized team for labeling leukocytes. Despite the fact that LeukoScan involves the i.v. injection of mouse proteins, no anaphylactic or other hypersensitivity reactions were observed.

^{99m}Tc ciprofloxacin (*Infecton*) is also being used to image infection. Ciprofloxacin is a broad-spectrum fluoroquinolone antibiotic that inhibits DNA gyrase and/or topoisomerase IV of bacteria. Patients receive ^{99m}Tc ciprofloxacin 10 mCi, and images are obtained at 1, at 3–4, and, occasionally, at 24 h postinjection. ^{99m}Tc ciprofloxacin may be useful in distinguishing infection from inflammation. Early images of noninfectious rheumatologic inflammatory conditions were positive, but activity decreased with time [69].

^{111}In - and ^{99m}Tc -labeled chemotactic peptide analogs have been used for detecting and localizing infections. Imaging can be performed at less than 3 h postinjection, which compares favorably with the 18–24 h or more for most other agents [54].

Labeled liposomes have been used for scintigraphic imaging of infection and inflammation [70]. Boerman et al. [71] used ^{111}In -labeled sterically stabilized liposomes (long circulating) in rats and showed that the clearance of this agent is similar to that of ^{111}In IgG. The uptake in abscess was twice as high as that of IgG and the abscess

was visualized as early as 1 h post injection. ^{99m}Tc nanocolloid has also been tried but has not gained wide acceptance.

F-18 fluorodeoxyglucose (FDG-PET) has emerged as an important diagnostic agent for infectious and noninfectious soft tissue and skeletal inflammations including inflammatory bowel disease, fevers of unknown origin, rheumatologic disorders, tuberculosis infection, fungal infection, pneumonia, abscess, postarthroplasty infections, chronic and vertebral osteomyelitis, sarcoidosis, and chemotherapy-induced pneumonitis [72–74]. Inflammatory conditions show high FDG uptake which is related to increased glucose metabolism that is produced by stimulated inflammatory cells, macrophage proliferation, and healing [75]. While uptake of FDG continues to increase at malignant sites for several hours, as can be shown by an incremental increase of the standardized uptake values (SUV), inflammatory lesions peak at approximately 60 min, and their SUV either stabilize or decline thereafter. This difference in the behavior of FDG in malignant versus inflammatory cells can be explained best by the varying levels of enzymes that degrade deoxyglucose-6-phosphate in the respective cells. Glucose-6-phosphatase dephosphorylates intracellular FDG-6-phosphate, allowing it to leave the cell. It has been shown that most tumor cells have low levels of this enzyme, while its expression is high in the mononuclear cells [76–85]. For this reason, imaging at 2 time points after administration of FDG may prove to be important in differentiating between these two common disorders.

4.8 Infection Imaging

Diagnosis and localization of infection by clinical and laboratory methods is often difficult. The results frequently are nonspecific and imaging may be needed. Imaging of infection may be achieved by either nuclear medicine or other strictly morphological methods. Several nuclear medicine modalities are used to diagnose and localize soft tissue and skeletal infections. These include ^{111}In -labeled white blood cells,



Fig. 4.8 Ultrasonographic study of a patient with abdominal pain and malaise. The study helped make the diagnosis of abdominal abscess (*arrow*) and provided accurate localization

^{67}Ga citrate, IgG polyclonal antibodies labeled with ^{111}In or $^{99\text{m}}\text{Tc}$, monoclonal antibodies such as antigranulocyte antibodies, $^{99\text{m}}\text{Tc}$ HMPAO-labeled white blood cells, $^{99\text{m}}\text{Tc}$ nanocolloid, $^{99\text{m}}\text{Tc}$ -DMSA, $^{99\text{m}}\text{Tc}$ -glucoheptonate, $^{99\text{m}}\text{Tc}$ -MDP multiphase bone scan, ^{111}In -labeled chemotactic peptide analogs, and F-18-FDG. X-ray, CT, MRI, and ultrasonography are other modalities useful in the diagnosis and localization of both soft tissue and skeletal inflammations. These studies are complementary to the physiological modalities of nuclear medicine.

4.8.1 Imaging of Soft Tissue Infections

The strategy for imaging soft tissue infections depends on the pathophysiological and clinical

features, including whether localizing signs and symptoms are present and the location and duration of the suspected infection.

4.8.2 Localizing Signs Present

4.8.2.1 Imaging Abdominal Infections

Abdominal abscess: Rapid and accurate diagnosis of an abdominal abscess is crucial. The mortality from untreated abscesses approaches 40 % and may reach 100 % in some series. The mortality among patients treated reaches 11 % [86–93]. Delayed diagnosis is associated with higher mortality in spite of treatment. If localizing signs suggest abdominal infection, morphological modalities, predominantly ultrasound (Fig. 4.8) and CT (Fig. 4.9), may be used first, depending on the location of suspected infection in the abdomen.

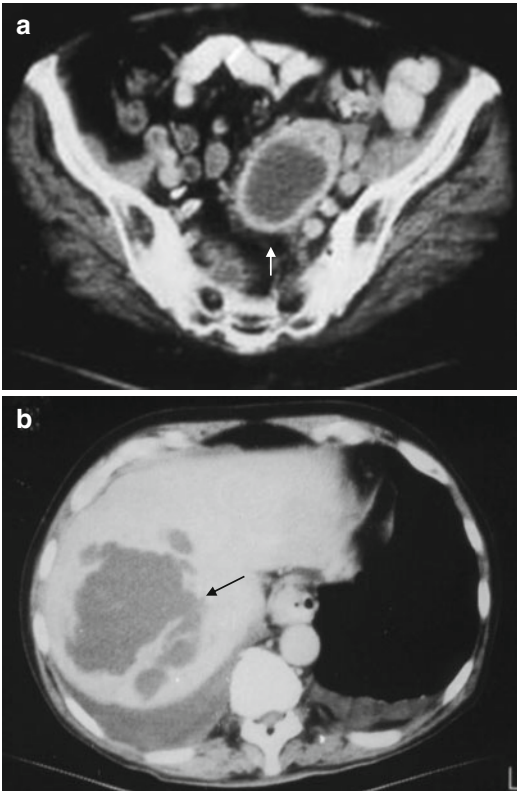


Fig. 4.9 Representative images of CT scans of the abdomen illustrating (a) periappendicular abscess (arrow) and (b) hepatic abscess (arrow)

Standard radiographs have low sensitivity, although when seen, findings are specific.

The advantages of these modalities are numerous, but most importantly, they provide quick results and adequate anatomic details. These studies can be used to guide needle aspiration and abscess drainage. Ultrasound can be used portably for critically ill patients. One of the major limitations of these modalities is the inability to differentiate infected from noninfected tissue abnormalities, particularly in early stages of infection (phlegmon) before formation of abscesses.

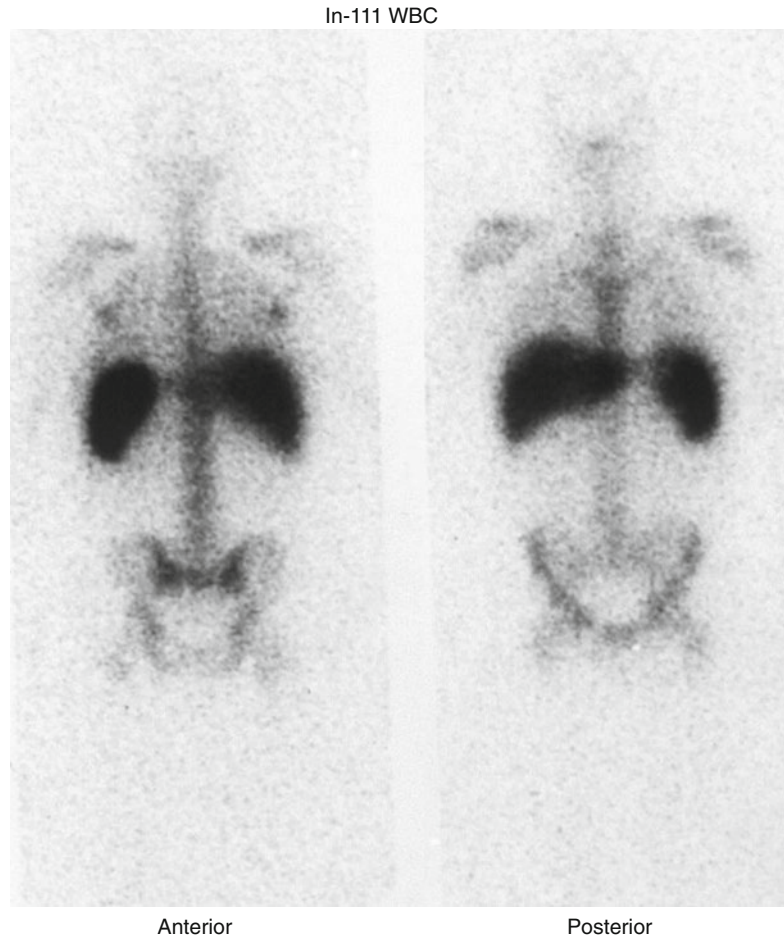
The diagnostic accuracy of these morphological modalities may be compromised in cancer patients, and the evaluation of studies that use these techniques may be difficult. This is because the interpretation of these modalities depends on

the presence of normal anatomical markers, which may be altered or obliterated by either the cancer treatment or the cancer itself [94]. For example, both CT and MRI are often of little value in distinguishing posttreatment scarring from recurrent tumor.

When the results of the morphological modalities are inconclusive, nuclear medicine techniques may be used to detect abdominal infections. The ability to image the entire body is the major advantage of nuclear medicine modalities (Fig. 4.10). Hence, radionuclide techniques are often used in cases with no localizing signs. In one study, 16 % of patients suspected of having abdominal infection in fact had extra-abdominal infections as seen on ^{111}In leukocyte scans [95]. Accordingly, negative morphological modalities, when used first, may be followed by whole-body nuclear imaging. Labeled WBC studies are the most specific for acute infections (Figs. 4.11 and 4.12). Ga-67 is more suitable for infection of longer duration (Fig. 4.13). $^{99\text{m}}\text{Tc}$ HMPAO-labeled WBCs frequently are used in critically ill patients [39] after US and/or CT have yielded inconclusive results. It is worthy of note that $^{99\text{m}}\text{Tc}$ HMPAO-labeled WBCs provide quicker results than ^{67}Ga - or ^{111}In -labeled WBCs. Minoja et al. [96] reported a sensitivity of 95 %, a specificity of 91 %, and an accuracy of 94 % for $^{99\text{m}}\text{Tc}$ -labeled WBC scanning in intensive care unit patients with occult infections. Gallium-67 scan has been reported to have better diagnostic specificity than the C-reactive protein test for abdominal infections [97].

Inflammatory Bowel Disease: Upright chest radiography and abdominal series, barium enema, and upper GI CT scanning, MRI, and ultrasonography are the main imaging modalities used for the diagnosis. CT scanning and ultrasonography are best for demonstrating complications such as intra-abdominal abscesses and fistulas. Evaluation of the extent of the disease and disease activity is often difficult. A wide variety of approaches depicting the different stages of the inflammatory response have been developed. Nonspecific radiolabeled compounds, such as ^{67}Ga citrate and radiolabeled polyclonal

Fig. 4.10 Whole-body 24 h ^{111}In -labeled leukocyte scan obtained in a patient with a 10-day history of fever and no localizing signs. Anterior and posterior images reveal physiological uptake in the bone marrow, liver, and spleen with no abnormal accumulation of labeled cells



human immunoglobulin, accumulate in inflammatory foci due to enhanced vascular permeability. Specific accumulation of radiolabeled compounds in inflammatory lesions results from binding to activated endothelium (e.g., radiolabeled anti-E-selectin), the enhanced influx of leukocytes (e.g., radiolabeled autologous leukocytes, antigranulocyte antibodies, or cytokines), the enhanced glucose uptake by activated leukocytes (18F-fluorodeoxyglucose), or direct binding to microorganisms (e.g., radiolabeled ciprofloxacin or antimicrobial peptides). Scintigraphy using autologous leukocytes, labeled with ^{111}In or $^{99\text{m}}\text{Tc}$, is still considered the “gold standard” nuclear medicine technique for the imaging of infection and inflammation, but the range of radiolabeled compounds available for this indica-

tion is still expanding. Recently, positron emission tomography with 18F-fluorodeoxyglucose has been shown to delineate various infectious and inflammatory disorders with high sensitivity. In a study [98], gallium, magnetic resonance imaging (MRI), and PET-FDG were compared for their ability to detect disease activity. PET-FDG showed more than twice as many lesions in the abdomen of patients with Crohn’s disease as did gallium. Not all lesions on MRI were FDG positive, suggesting they might represent areas of prior inflammation.

4.8.2.2 Imaging Chest Infections

The role of the chest X-ray cannot be overemphasized. The chest X-ray should be used as the initial imaging modality for most chest pathologies.

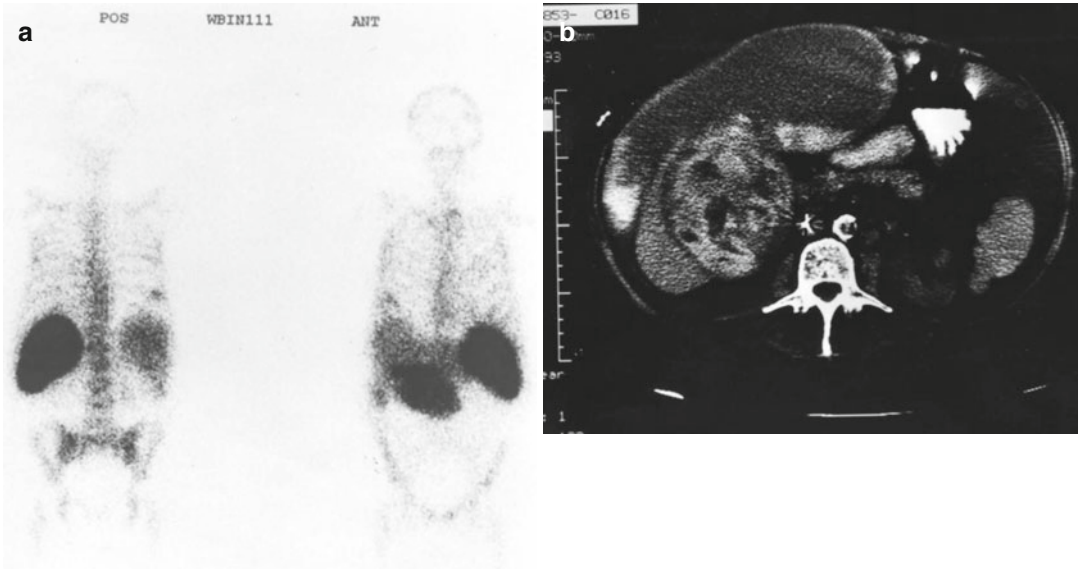


Fig. 4.11 (a, b) ^{111}In -labeled leukocyte study (a) shows a large acute abdominal abscess (arrow) corresponding to the finding (arrow) on CT (b)



Fig. 4.12 ^{111}In -labeled leukocyte scan posterior projection of the abdomen demonstrating two foci (arrows) of abnormal accumulation of labeled cells at the ends of a vascular graft indication infection of the graft

In many instances, however, an additional modality is needed to evaluate certain chest conditions including infections.

Although CT often clearly depicts chest pathology including infections, ^{67}Ga still is commonly used in such cases. ^{111}In leukocytes have limited utility for chest infections. Simon et al. [99] studied ^{67}Ga imaging in a variety of pulmonary disorders and found excellent sensitivity and specificity (Table 4.6). Gallium-67 has also been widely used in AIDS patients to detect PCP (Fig. 4.14). It is highly sensitive and correlates with the response to therapy. In a study comparing ^{67}Ga , bronchial washing, and transbronchial biopsy in 19 patients with PCP and AIDS, ^{67}Ga and bronchial washing were 100 % sensitive compared with 81 % for transbronchial biopsy [101]. ^{67}Ga is also valuable in idiopathic pulmonary fibrosis, sarcoidosis, and amiodarone toxicity [102, 103]. It is also useful in monitoring response to therapy of other infections including tuberculosis (Fig. 4.15).

^{111}In WBC imaging is less helpful, as the specificity of abnormal pulmonary uptake (either focal or diffuse) is very low. Noninfectious problems that cause abnormal uptake include congestive heart failure, atelectasis, pulmonary embolism, ARDS, and idiopathic conditions [104].

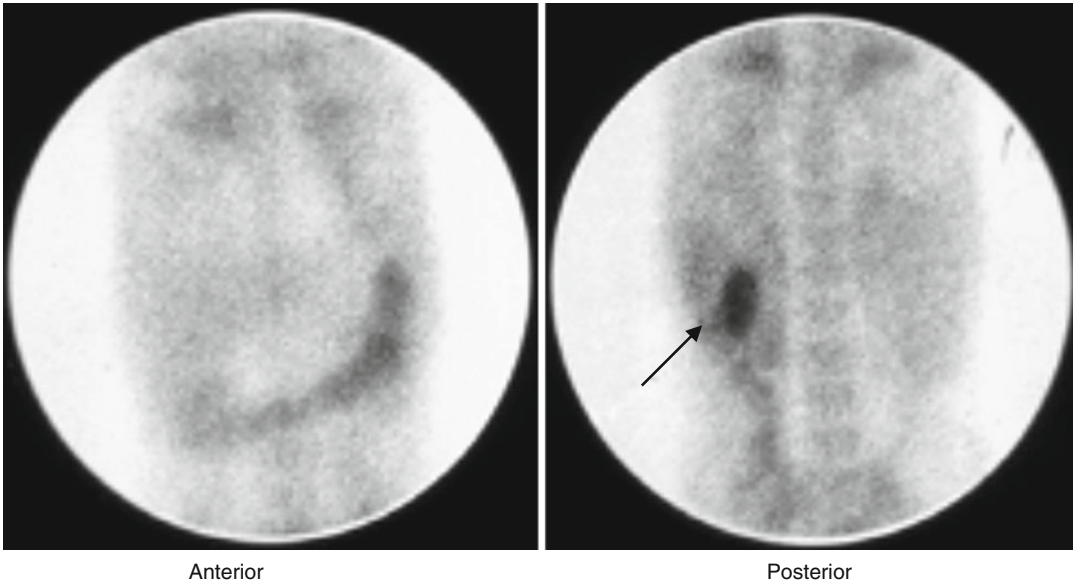


Fig. 4.13 A 72 h gallium-67 image of abdomen anterior and posterior projections for a 21-year-old female with a 6-week history of intermittent fever. No localizing signs

were reported. The images demonstrate increased accumulation of gallium-67 in a perirenal abscess (*arrow*) seen in posterior view

Table 4.6 ⁶⁷Ga findings in patients with lung pathologies including infections

Pathology	Patients (n)	Ga negative (%)	Ga positive (%)
Normal	100	100	–
Active tuberculosis	197	3	97
Inactive tuberculosis	32	100	–
Pulmonary abscess	18	–	100
Asbestosis	12	–	100
Cancer	264	10	90

From [100]

4.8.2.3 Imaging Renal Infections

The CT scan has good sensitivity and specificity in the diagnosis of renal infections. Ultrasound has been used frequently to evaluate the kidneys with suspected infections, even though it is not sensitive. It is used primarily to screen for obstruction or abscess when resolution of UTI is slower than expected with treatment. The sensitivity of US has been shown to be less than 60 % [105] and is significantly inferior to that of cortical scintigraphy

(sensitivity of 86 % and specificity of 81 % using ^{99m}Tc-glucoheptonate). Positive ultrasonography can obviate the need for DMSA; however, because of a large number of false-negative results with reported sensitivities of 42–58 % and underestimation of the pyelonephritis lesions, ultrasonography cannot replace ^{99m}Tc-DMSA [106]. To date ^{99m}Tc-DMSA is considered the most sensitive method for the detection of acute pyelonephritis in children (Fig. 4.16). It also permits the photopenic area to be calculated as the inflammatory volume which correlates with the severity of infection and the possibility of scar formation even though some of the defects detected might be too small to be clinically significant. Currently US is recommended as the initial imaging modalities by the American Academy of Pediatrics and the National Institute for Health and Clinical Excellence (NICE) in atypical and recurrent UTI in pediatric age group [107, 108]. The pathophysiological basis of the ability of Doppler sonography in detecting acute pyelonephritis is the fact that in the acute phase of pyelonephritis the, focal decrease of renal perfusion due to edema causes vascular compression, intravascular granulocyte

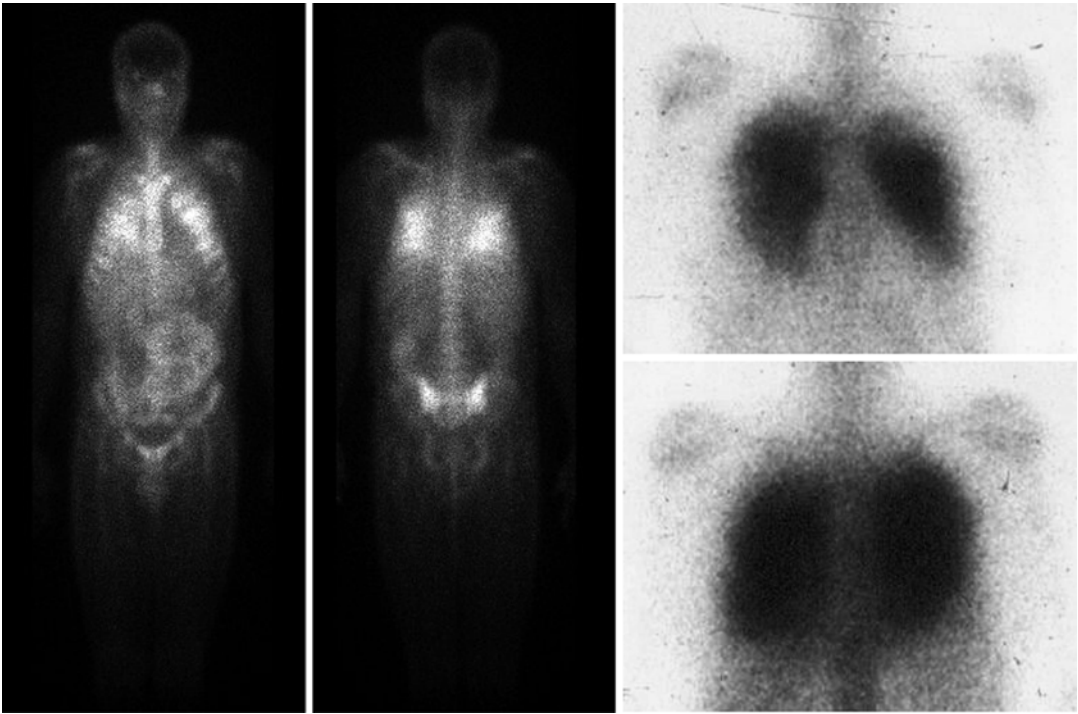


Fig. 4.14 Gallium-67 images of an AIDS patient with a 5-week history of fever. Images show diffuse uptake in both lungs illustrating the typical pattern of gallium-67 in PCP

aggregation, or both, leading to capillary and arteriolar occlusion facilitating the detection of these hypovascular areas [109].

4.8.2.4 Imaging of Skeletal Infection

Several imaging techniques are being utilized for the detection of osteomyelitis including the standard radiograph, computerized tomography, magnetic resonance imaging, and several nuclear medicine modalities. The choice of modality depends on the clinical presentation, particularly its duration, the site of suspected infection, and whether the site of suspected infection has been affected by previous pathology. The pathophysiology of skeletal inflammations and relevant scintigraphic considerations are discussed in detail in Chap. 5, on the musculoskeletal system.

4.8.3 No Localizing Signs Present

When no localizing clinical signs are present, which is common in cancer and immunosup-

pressed patients, nuclear medicine procedures are often the imaging modalities chosen. The ability to screen the entire body is particularly important for many such cases.

The optimal choice of radiotracer again depends on the duration of infection (Fig. 4.17). ^{111}In -labeled white blood cells are the most specific for acute infections, but false-positive results have been reported with some tumors, swallowed infected sputum, GI bleeding, and sterile inflammation. False-negative results have been reported in infections present for more than 2 weeks. More rarely, such false-negative results occur for infections present for only 1 week. Gallium-67 is less specific than labeled WBCs, as it is taken up by many tumors and by sterile inflammation. Several radiolabeled antibody preparations and a radiolabeled antibacterial agent have been introduced and evaluated, but none of these have been used widely. Labeled antibody scintigraphy uses antigranulocyte agents, most commonly intact murine immunoglobulin G (IgG) antibodies against normal

cross-reactive antigen-95 (anti-NCA-95, ^{99m}Tc -BW250/183, ^{99m}Tc -besilesomab [Scintimun[®]]) and the murine Fab fragment of the IgG antibody directed against the glycoprotein cross-reactive antigen-90 (anti-NCA-90, ^{99m}Tc -sulesomab, LeukoScan[®]). ^{99m}Tc -IgG scintigraphy is a highly sensitive technique for the recognition of infec-

tion but has a low specificity PET-FDG has now taken the place occupied by citrate of Gallium-67. Visualization of inflammatory lesions does not just rely on the presence of immune cells, but uptake requires the activation of these immune cells. FDG-PET reveals infectious and noninfectious inflammatory diseases as well as malignant

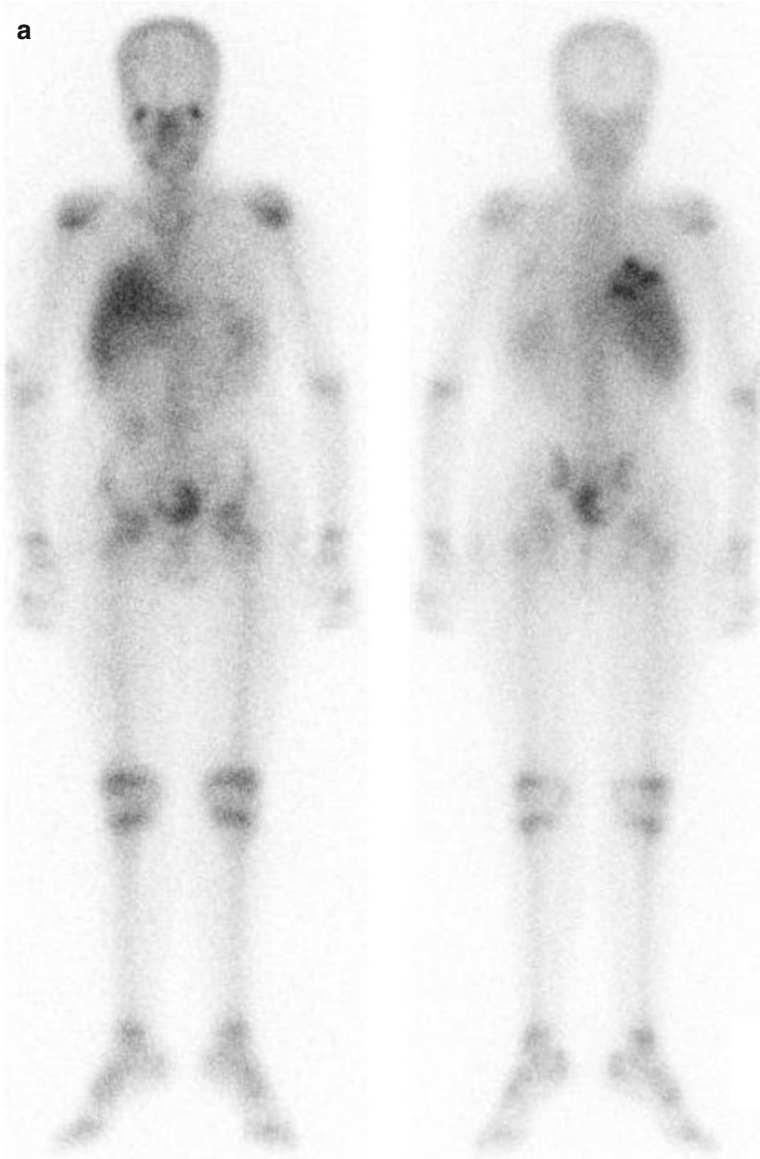


Fig. 4.15 (a, b) Gallium-67 studies of a patient with tuberculosis. Initial study (a) showing abnormal uptake of the right lung (*arrows*) which disappeared on follow-up

study (b) 3 months after starting therapy, indicating excellent response to treatment

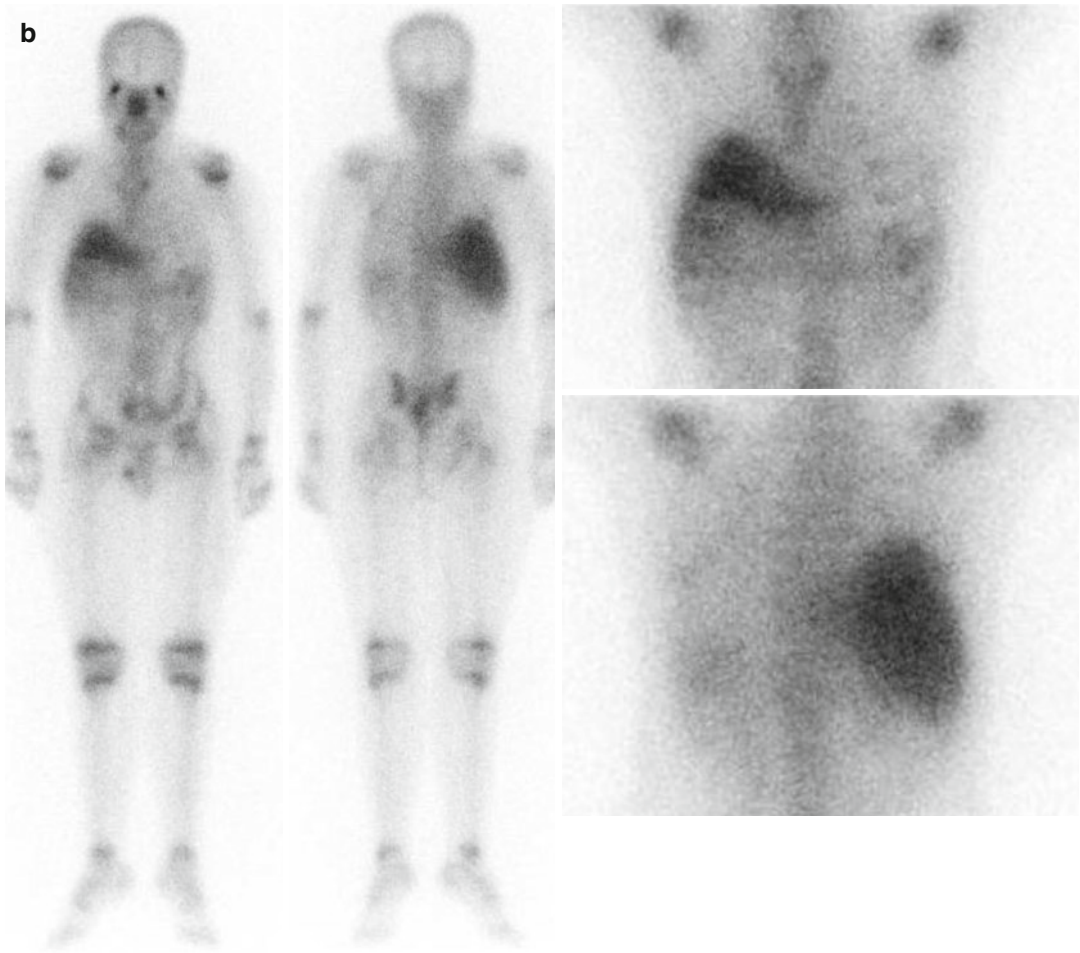


Fig. 4.15 (continued)

diseases; all are causes of fever of unknown origin. Recent studies support the use of FDG-PET in the patient with FUO [72, 73, 110]. FDG is sensitive and its short half-life does not delay the performance of any additional radionuclide studies that might be needed.

Various chronic infectious diseases that are frequent clinical challenges are better diagnosed with the use of PET, particularly when this imaging is combined with CT. For noninfectious inflammatory diseases, FDG-PET has proved particularly helpful for the diagnosis and management of large vessels arteritis and inflammatory bowel disease [74, 111, 112].

Correlation with morphological modalities after successful radionuclide localization of infection can be of great help. For example, this correlation provides anatomical information prior to surgical interventions. Morphological modalities are useful in the management of inflammatory diseases particularly if localizing signs are present. They have the very important advantages of better spatial resolution than nuclear medicine modalities. X-rays, CT, MRI, and US usually yield fast results but unfortunately may not distinguish infected from noninfected tissue. Figure 4.17 illustrates suggested algorithms for the diagnosis of soft tissue infections.

Fig. 4.16 ^{99m}Tc -DMSA study in a patient with chronic pyelonephritis and significant urine outflow obstruction. Note the irregularly thinned cortex and the dilated pelvocalyceal system on the left affected kidney

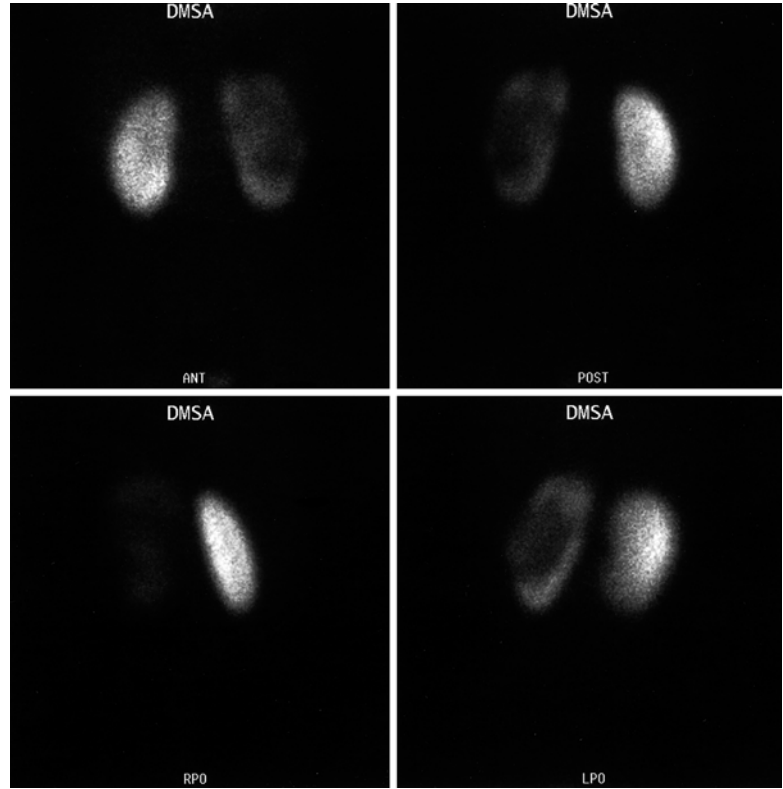


Fig. 4.17 Suggested diagnostic algorithm for soft tissue infections. Note that in case of suspected renal infection, ^{99m}Tc -DMSA scan is preferred; in infections of relatively long duration, labeled WBC may be used, but if negative, ^{67}Ga or other labeled antibodies should follow before excluding chronic active infection due to possible false-negative results with labeled WBC

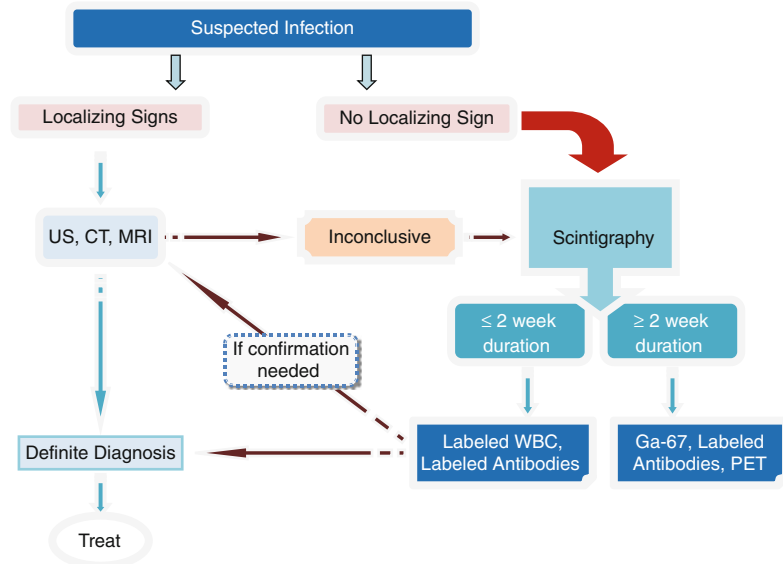


Table 4.7 Correlation of pathophysiological features and scintigraphic findings of infection

Pathological change at the site of infection	Scintigraphic pattern
Hyperemia	Locally increased accumulation of several radiotracers, increased flow and blood pool activity on bone scan; hyperemic pattern on delayed bone images may be present with soft tissue infection
Increased vascular permeability	Increased migration of WBCs, increased accumulation of ^{67}Ga , increased uptake of radiolabeled antibodies
Increased migration of WBCs and chemotaxis	Increased accumulation of labeled WBCs
Increased secretion of iron-containing globulin by injured and stimulated WBCs	Increased accumulation of ^{67}Ga
Localized areas of renal parenchymal damage in pyelonephritis	Areas of reduced or absent DMSA uptake
Dilation of PC system in pyelonephritis	Prominent pelvocalyceal system on DMSA images
Formation of woven bone	Increased uptake of $^{99\text{mTc}}\text{-MDP}$ with prolonged accumulation of radiotracer
Increased expression of glucose transporters on cell surface	Increased uptake of $^{18}\text{F}\text{-FDG}$

4.9 Summary

Many morphological and functional imaging modalities are available to help diagnose and localize inflammation of the soft tissue and bone. It is clear that no single technique is ideal in all situations. The choice depends on several factors, including whether localizing signs are present, the site of possible infection, whether anatomy is normal or altered by surgery or trauma, the duration of symptoms and signs, and the presence of other underlying diseases such as cancer. For physicians, understanding the pathophysiological changes is crucial for deciding on an appropriate diagnostic strategy. Understanding pathophysiological changes also helps the nuclear physician to recognize and explain the scintigraphic patterns of inflammatory conditions (Table 4.7 summarizes common examples). Further evaluation of PET in diagnosis, localizing, and follow-up of inflammations is a current interest. The discovery of new radiopharmaceuticals that will be ideal for more specific imaging of inflammation is an important topic for future research.

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