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From diagnosis to management: Navigating the complex terrain of granulomatous disease

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ABSTRACT

In the realm of granulomatous diseases, the convergence of pathophysiology, epidemiology, and therapeutic strategies presents a labyrinth of complexity with far-reaching clinical implications. This review embarks on a scholarly expedition through the intricate landscape of granulomatous inflammation, dissecting the multifaceted presentations ranging from infectious etiologies to enigmatic autoimmune disorders. With a discerning eye on recent advancements and literature, we unravel the nuanced interactions between host defenses and granuloma formation, alongside the pivotal role of cytokines and mononuclear cells in orchestrating these responses. Beyond a mere academic exercise, our exploration delves into the clinical juxtaposition of common and esoteric causes, offering a panoramic view on diagnostic methodologies that straddle the traditional and the innovative. The management of granulomatous diseases, often a tightrope walk balancing efficacy and toxicity, is critically examined, shedding light on conventional and emerging therapies that promise to reshape the therapeutic landscape. By weaving together threads of current research, this review aspires to enhance the understanding of granulomatous diseases and catalyze future inquiries into their mysteries. In doing so, it stands as a beacon for clinicians.

Keywords: Granulomatous Disease, granuloma, cytokines, mononuclear cell, tuberculosis, brucellosis, sarcoidosis, Q fever, Wegener's.

Granulomas are chronic inflammatory limited lesions of mainly mononuclear cells that develop in response to antigenic stimuli and are formed due to an inflammatory reaction in body tissues. A granuloma is characterized by a central accumulation of mononuclear cells, mainly macrophages, with a surrounding framework of lymphocytes and fibroblasts. The lesions are distinct from nearby uninvolved tissue.

In the early stages of granuloma development, lesions may appear as perforated histiocytes or lymphocyte clusters. Granulomas develop by stimulation of mononuclear cells by various cytokines. Activated macrophages are transformed to resemble epithelial cells (epithelioid cells), which characteristically have abundant, pale cytoplasm. Adjacent macrophages can fuse to form giant multinucleated cells.

The cells within the granuloma can secrete various proteins. For example, epithelioid cells from patients with sarcoidosis secrete lysozyme, collagenase, and angiotensin-converting enzyme (ACE).

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Immune granulomas such as epithelioid cell granulomas and hypersensitivity granulomas are specific granulomas. The causative agent may not be seen in particular granulomas, but a microscopic diagnosis can be made based on the characteristics of the granulomatous inflammation.[1] Some causative agents may cause lesions of the three main types of inflammation (exudative, necrotic, and proliferative). Of these, only proliferative (granulomatous) lesions can be specific. Necrotic or exudative inflammations are not exact, regardless of the causative agent.

Immune granuloma formation is the result of a late hypersensitivity reaction involving T-lymphocytes. Alive agents that activate T-lymphocytes and other causes lead to the formation of immune granulomas. Most of the living agents that cause this picture are intracellular and slowly proliferating microorganisms.[2]

Non-immune granulomas (foreign body granulomas) are the granulomatous reaction that occurs in the presence of larger bodies or indigestible substances than a macrophage can phagocytize. The reacting bodies or substances do not stimulate the immune system because they do not contain antigens. They often cause a "foreign body reaction" by physical or chemical irritation. Objects that cause granulomatous reactions are categorized into two groups.[1]

1-Endogenous: hair, keratin, cholesterin crystals, sodium urate (gout), dead bone tissue in osteomyelitis (sequestrate).

2-Exogenous: silicones (asbestos), berylliosis, sutures, parasite eggs, etc.

Granuloma Types

Caseating granuloma comprises epithelioid cells, giant cells, and lymphocytes and is characterized by central necrosis. Tuberculosis, fungal infection, and rheumatoid arthritis are examples of this group.

Non-caseating granuloma consists of epithelioid cells, giant cells, and lymphocytes. It does not contain central necrosis. Sarcoidosis, Beryllium, and Crohn's disease can be given as an example to this group.

Fibrin-rich granuloma shows a vacuole surrounded by fibrin in the center and epithelioid cells around it. It can be seen in Q fever, Hodgkin's disease, and giant cell arteritis.

Lipogranulomas show lipid vacuoles in the center and are associated with mineral fat intake.[3]

Granulomatous Involvement

-Skin Lesions (SLE, Psoriasis, Sarcoidosis, Cat Scratch Disease)

-Lymphadenopathy (Lymphomas, Sarcoidosis, Tuberculosis)

-Eye and CNS Involvement (Sarcoidosis, Lymphoma, Whipple's Disease)

-Heart Involvement (Q Fever, Sarcoidosis)

-GI Involvement (Whipple's Disease, Crohn's Disease, Ulcerative Colitis, Tuberculosis, Typhoid Fever)

-Joint Involvement (SLE, Sarcoidosis, Brucella, Tuberculosis)

Causes of Granuloma

Infections

Tuberculosis, Brucella, Cat scratch disease, Lymphogranuloma Venerum, Paracoccidioidomycosis, Histoplasmosis, Aspergillosis, Cryptococcus neoformans, Leishmaniosis, Leprosy, Tularemia, CMV, EBV, Q fever

Autoimmune Diseases

Sarcoidosis, Ulcerative Colitis, Crohn's Disease, Primary Biliary Cirrhosis, Rheumatoid Arthritis, Systemic Lupus Erythematosus, Temporal Arteritis, Wegener's Granulomatosis, Churg-Straus Disease

Foreign body drugs and toxins

Allopurinol, methyldopa, sulfonamides, berylliosis, sutures, talc aluminum toxicity, Hypersensitive pneumonitis

Neoplastic

Lymphomas and carcinomas

Chronic Granulomatous Disease of Childhood

TUBERCULOSIS

Tuberculosis (TB) is a bacterial chronic infectious disease characterized by the formation of typical granulomas with caseation necrosis, which can affect almost every organ/tissue, especially the lungs. The causative agent of the disease is Mycobacterium tuberculosis, a genus of mycobacteria.[4,5]

Mycobacterium tuberculosis is an intracellular bacillus in the Mycobacteria class, immobile, non-spore, 1-4 mm in size. Although it is obligately aerobic, it is a resistant bacillus that can survive without reproducing with very little oxygen in the environment. It does not stain Gram stain. They do not release their stain after treatment with acid and alcohol (Acid and alcohol-resistant bacilli).

Mycobacterium tuberculosis grows in a unique

enriched medium; colonies form in 3 - 8 weeks, and the growth temperature is 35 - 37 °C. They like oxygenated environments and are not resistant to heat and sunlight. They can remain viable in dry sputum for 6-8 months when protected from sunlight.

Various respiratory maneuvers have different potential to create particles (aerosols) in the air. Speaking produces 0-210, coughing 0-3,500, and sneezing 4,500-1,000,000,000 particles.[6]

Tuberculosis is transmitted by inhalation of particles (droplet nuclei) emitted by a tuberculosis patient, which are 1-5 microns in size and contain 1-3 viable bacilli. An untreated TB patient infects about 10-15 people each year. Infection and disease development after exposure to tuberculous bacilli The Contact - Infection - Disease cycle is shown in Figure 1.

In people not infected with TB bacilli and living in a high TB prevalence area, the likelihood of encountering TB bacilli, the duration of the encounter, and the susceptibility of the person are risk factors for becoming infected with TB bacilli.

Risk factors for the occurrence of active TB disease in people infected with TB bacilli are AIDS (170 times the risk), HIV infection (113 times the risk), Cancer, Diabetes Mellitus (3-16 times the risk), Drug addicts, Chronic renal failure, Low body weight (10% less than standard), Length of time after infection.

Tuberculosis Pathogenesis Stages

Phase I First Meeting (Figure 2).[7]

Phase II: Early Proliferation and Expansion (Figure 2).[7]

Phase III: Development of Cellular Immunity and Late Hypersensitivity (Figure 3).[7]

Stage IV: Lymphedema, Cavitation, Bacilli Proliferation and Endobronchial Invasion (Figure 4).[7]

Progressive Primary Tuberculosis (Pediatric Tuberculosis)

Following primary infection, 5% of infected patients develop progressive primary disease. In communities where TB is prevalent, primary TB is more common in childhood and the newborn period.[8] It is more common in immunocompromised patients, such as those with advanced HIV (Figure 5).[10]

Post-primary Tuberculosis (Adult-type Tuberculosis)

It usually occurs weeks or years after the primary infection with activation of latent infection in the upper zones of the lungs.[9]

Post-primary tuberculosis is primarily an adult disease (Figure 5).

Pulmonary tuberculosis

Is a disease picture involving the lung parenchyma. Tuberculosis disease affects the lungs in 70-80% of

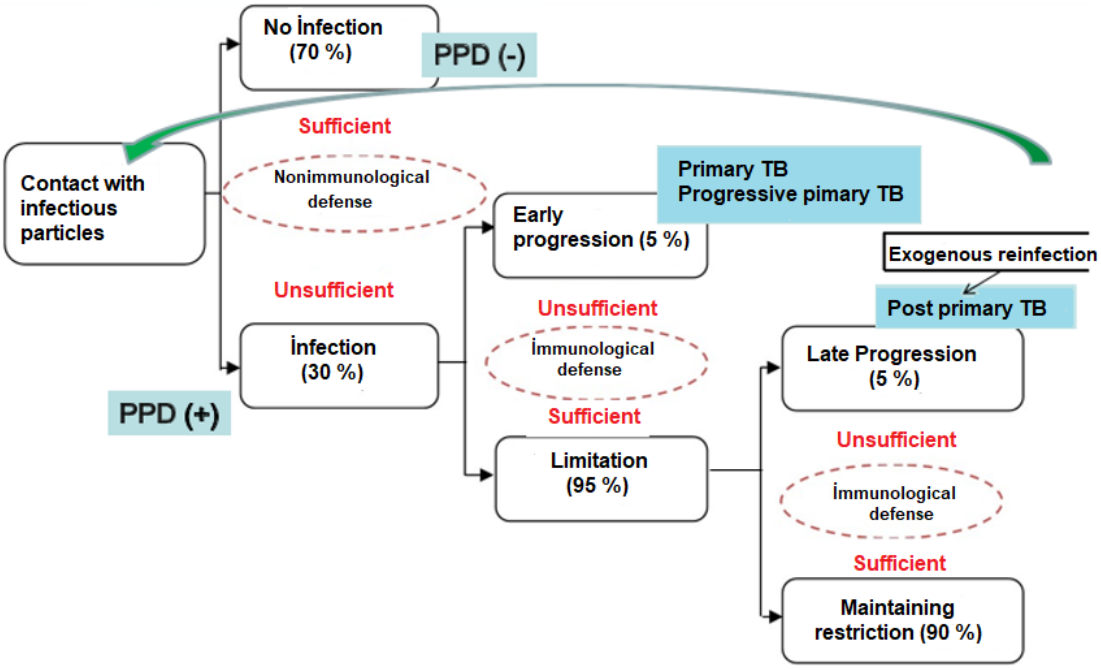

Figure 1. Contact - Infection - Disease cycle

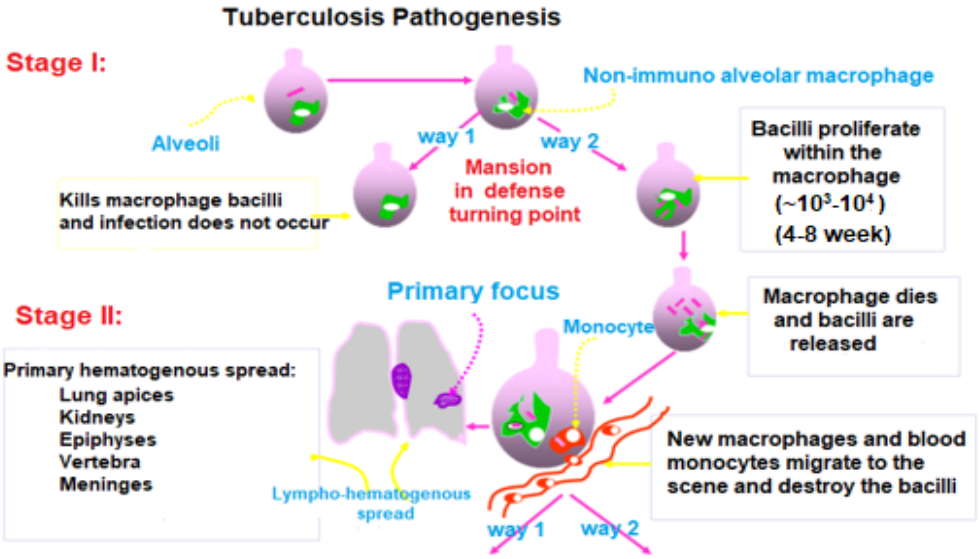

Figure 2. Figure 3. Pathogenesis of Tuberculosis.[7]

cases. Pleural effusion or mediastinal lymph node enlargement without involvement of the parenchyma is considered extrapulmonary.

Extrapulmonary tuberculosis

Is defined as patients with ARB in samples taken from organs other than the lung parenchyma or with histologic and clinical findings compatible with tuberculosis. Extrapulmonary Tuberculosis involvement sites include the pleura, central nervous system, lymphatic system, genitourinary system, bone, and joints.[11]

Clinical Presentation

Tuberculosis patients may present with respiratory symptoms such as cough, sputum production, hemoptysis, chest pain, back and side pain, shortness of breath, hoarseness and/or systemic symptoms such as fever (intermittent), night sweats, loss of appetite, weight loss, weakness, fatigue, and organ-specific symptoms (LAP, hematuria, joint swelling, etc.).

Patients with cough lasting more than three weeks and whose pulmonary findings do not improve with antibiotic treatment should be investigated for tuberculosis. There is no respiratory system physical examination finding specific to tuberculosis. If the

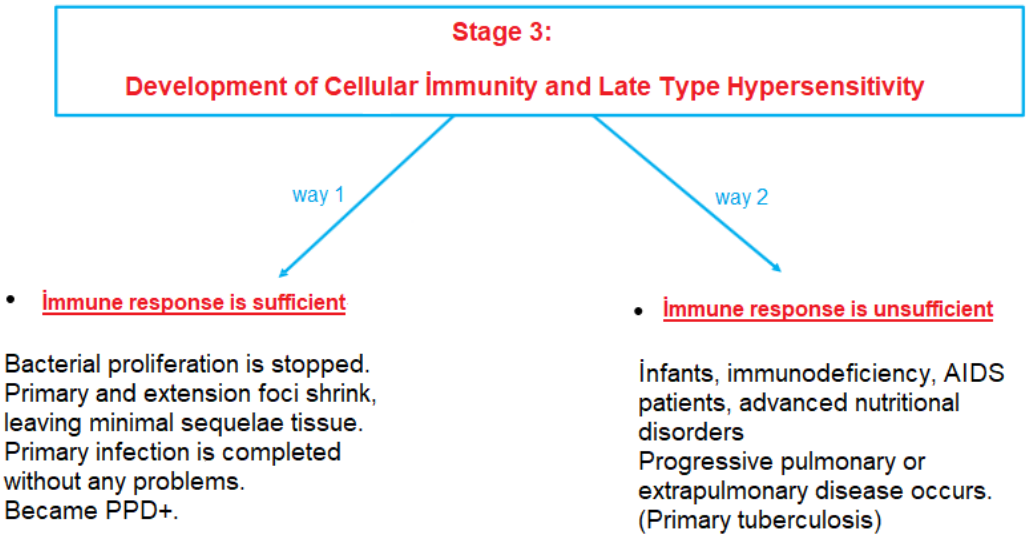

Figure 3. Pathogenesis of Tuberculosis.[7]

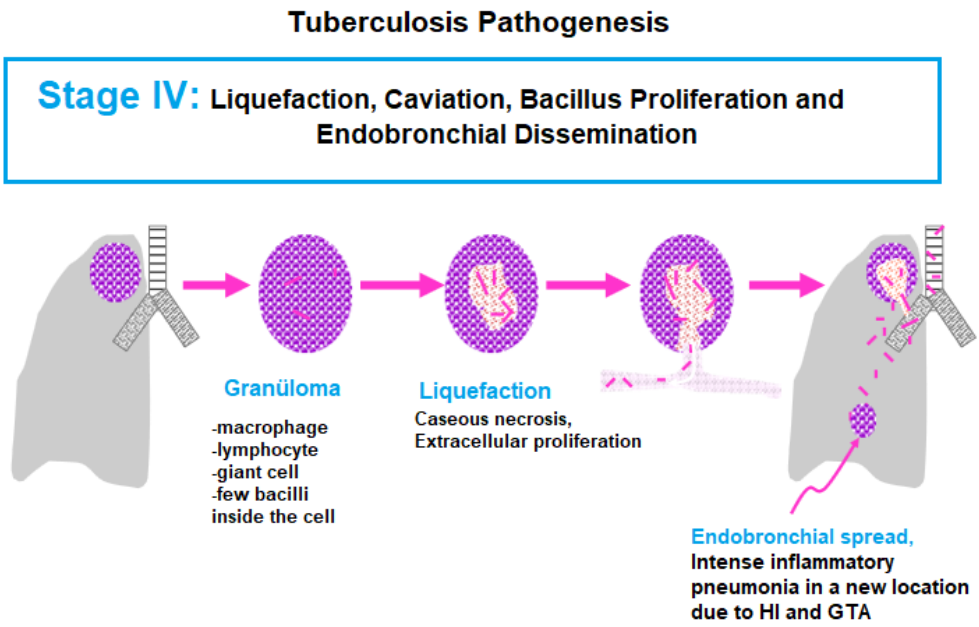

Figure 4. Pathogenesis of Tuberculosis.[7]

consolidation area is located close to the chest wall, rales may be heard in the background of bronchial sound. Amphoric sounds may be heard in patients with cavitary lesions.

Diagnosis

Bacteriologic diagnosis is essential in tuberculosis. Specimens that may be examined (Sputum, induced sputum, fasting gastric juice, bronchoscopic aspiration fluid, CSF, pleural fluid, urine, joint fluid, biopsy material, etc.).

Microscopy

An ARB examination with Ziehl-Neelsen staining in the morning sputum was collected on three consecutive days.

Culture

Inoculation of the microscopically examined material on Lowenstein-Jensen solid and/or automated liquid media. Production of tubercle bacilli in culture is the gold standard diagnostic method.[12]

Drug susceptibility test

Investigation of the susceptibility of the cultures to the antituberculosis drugs used in treatment.

The presence of ARB on direct examination of sputum or other specimens does not confirm the diagnosis. Culture is more sensitive than microscopy (sensitivity 80-85%, specificity 98%).

Tuberculin Skin Test (TST) and Interferon Gamma Release Tests are not recommended to diagnose active

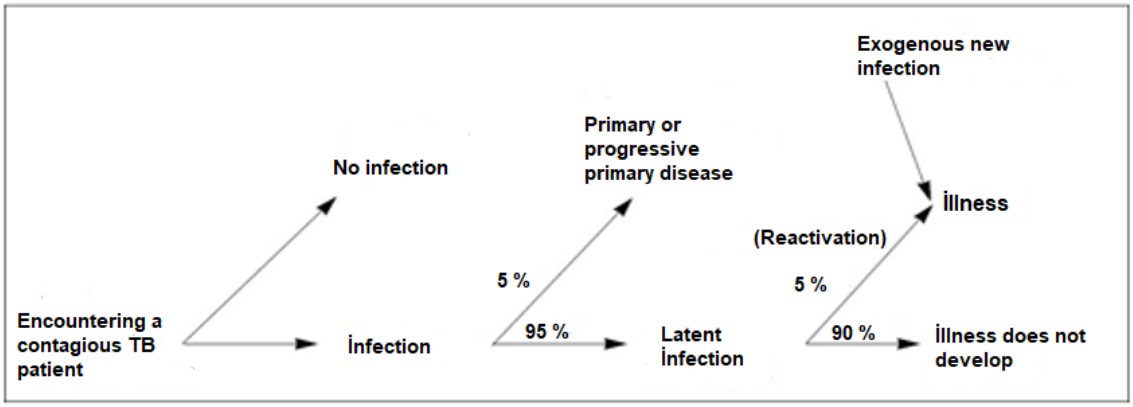

Figure 5. Tuberculous infection and disease development.[10]

TB in adults. These tests are positive in both latent TB infection and TB disease. They are positive as a result of late-type hypersensitivity due to TB bacilli.

TST shows whether a person is infected with TB bacilli; it does not give information about the disease. It may indirectly help in the diagnosis of the disease.[13] Criteria for evaluation of TCT reaction in Türkiye are as below.[14]

Patients Vaccinated with Bacille Calmette Guerin (BCG):

- 0-5 mm is considered negative.
- 6-14 mm is attributed to BCG.
- 15 mm and above are considered positive and considered infection.

Patients without BCG:

- 0-5 mm is considered negative.
- 6-9 mm is considered suspicious. The test is repeated after one week; if 6-9 mm is found again, it is considered negative.
- 10 mm and above is considered positive.
- In immunocompromised individuals, 5 mm or more is considered positive

Interferon-gamma (IFN-γ) regulates the cellular immune response to M. tuberculosis infection. IFN-γ release assays are in vitro tests that measure the cellular immune response to M. tuberculosis antigens. There are currently two commercial IFN-γ release assays. The ELISA-based assay is the QuantiFERON assay, which measures the level of IFN-γ released from T-cells, and the ELISPOT-based assay is the T-SPOT assay, which measures the number of T-cells producing IFN-γ.[10]

Nucleic acid amplification tests (NAAT) are another diagnostic method used to diagnose tuberculosis.[15] It is used in the diagnosis of tuberculosis, species identification in Mycobacteria, and detection of drug resistance.[16]

In histopathologic examination, granulomatous inflammation, especially caseification necrosis, in biopsy material taken from any tissue is a characteristic finding for tuberculosis.[17]

Chest X-ray

No radiologic finding is specific to Pulmonary Tuberculosis.[18] Imaging methods are not definitive diagnostic tests for TB. They are diagnostic aids. The main radiologic findings on chest radiography in post-primary tuberculosis are local exudative lesions, cavitation, bronchogenic extension, acute tuberculous pneumonia, local fibro calcified lesions, miliary tuberculosis, and tuberculoma. Cavities are found in approximately 40% of cases, and 95% of adult pulmonary tuberculosis is located in the apical, posterior segments of the upper or superior segments of the lower lobes.[19]

Thorax CT and HRCT (High-Resolution Computed Tomography) provide superiority in the early diagnosis of parenchymal diseases, early diagnosis of Miliary Tuberculosis, detection of Endobronchial lesions, detection of small cavities and parenchymal lesions covered by Pleural fluid.[20]

Treatment

Tuberculosis is a group-A notifiable infectious disease. It is reported to the Health Directorate within 24 hours of diagnosis.[21] First-generation drugs used to treat tuberculosis are Isoniazid, Ethambutol, Streptomycin, Pyrazinamide, and Rifampicin.[22]

In the Initial Phase (Initial Period), the treatment goal is to rapidly reduce bacilli with Early Bactericidal Activity and provide a Preventive Effect on Resistance Development.

In the Maintenance Phase, the treatment goal is to ensure sterilization by destroying all semi-dormant bacilli.

In the treatment of tuberculosis in new cases, a two-month 4-pack combination (Isoniazid + Rifampicin + Pyrazinamide + Ethambutol / Streptomycin) is used in the initial phase, and a month 2-pack combination (Isoniazid + Rifampicin) is used in the maintenance phase.

In case of relapse, in addition to the previous treatments, two months of 5-pack combination (Isoniazid + Rifampicin + Pyrazinamide + Ethambutol + Streptomycin) or one month of 4-pack combination treatment (Isoniazid + Rifampicin + Pyrazinamide + Ethambutol), and five months of 3-pack treatment (Isoniazid + Rifampicin + Ethambutol) in the maintenance phase.

Directly Supervised Treatment (DST) is mandatory in the hospital. The supervisor who administers the treatment monitors the patient to ensure that all TB medication is taken and makes sure that the patient takes the medication by standing over the patient while the patient takes it. When the patient has taken the medication, the patient and the supervisor sign the DST form.

DST in a tuberculosis dispensary

The dispensary has the lead or coordinating role in implementing DST during outpatient treatment. The TB dispensary physician must make the supervision plan for the patient, determine the person who will implement supervision, and determine where and when the medication will be administered.[23]

BRUCELLOSIS

Brucellosis is a bacterial zoonosis transmitted directly and indirectly from infected animals, especially domestic ruminants and swine, to humans.[24] Brucella strains cause human brucellosis. All Brucella bacteria are small, gram-negative, non-capsulated, non-spore, coma, or coccobacilli. These organisms are sensitive to sunlight, ionizing radiation, and moderate heat; they can be killed by boiling and pasteurization but resist freezing and desiccation. Brucella melitensis is transmitted by sheep, goats, and camels; B. abortus is transmitted mainly by cattle and bulls; B. suis is usually transmitted by pigs; and B. canis is transmitted by dogs.[25]

Brucellosis Clinical Presentation

Brucellosis invariably causes fever with profuse sweating, especially at night.[26] The fever is accompanied by muscle and joint pain in half or even all patients with brucellosis. In addition to the usual fever and sweating, patients become increasingly apathetic and fatigued, with anorexia, weight loss, non-specific muscle pain, headache, and lethargy. Musculoskeletal pain and physical examination findings in the periphery and spine (in 40% of cases) are the most common symptoms.[27] Osteomyelitis is more common in the lumbar and lower thoracic vertebrae than in the cervical and upper thoracic vertebrae. The joints affected by septic arthritis are the knee, hip, sacroiliac, shoulder, and sternoclavicular joints. Involvement may be monoarthritis or polyarthritis. Osteomyelitis may accompany septic arthritis.

One-fourth of patients have pneumonia, empyema, intrathoracic adenopathy, and lung abscess on chest X-ray, but dry cough with little change. One-fourth of patients have hepatosplenomegaly, and 10-20% have marked lymphadenopathy. Up to 10% of men develop acute epididymoorchitis, which must be differentiated from mumps and surgical conditions such as torsion. Prostatitis, inflammation of the seminal vesicles, salpingitis, and pyelonephritis also develop. Although teratogenicity has not been established, and abortion is less common in humans than in animals, there is a risk of fetal loss in infected pregnant women.[28] Neurotuberculosis, or lymphocytic meningoencephalitis, mimics non-infectious causes and can lead to intracerebral abscess, disorders of various cranial nerves, and mycotic aneurysms, is common.[29] Less than 1% of patients develop endocarditis, often involving the aortic valve (natural or artificial). Metastatic abscesses and inflammation develop in any part of the body. Remarkably, the female breasts and thyroid glands are frequently affected. Non-specific maculopapular tingling and other cutaneous manifestations are rare; if they occur, they are rarely reported by the patient.

Diagnosis

Isolation of bacteria from blood, CSF, bone marrow, joint fluid tissue aspirates, and biopsy material is diagnostic.[30]. In tissue biopsy specimens such as lymph nodes or liver, non-classified granulomas without acid/alcohol-resistant bacilli are found. The serologic examination is often the only positive laboratory finding in diagnosing brucellosis. IgM antibodies are formed early in acute infection, followed by IgG and IgA. In endemic areas or in case of occupational contact, an agglutination titer of 1/320 - 1/640 or more is diagnostic. In non-endemic areas, a titer of 1/160 and higher is considered significant. Repeat tests after 2-4 weeks may show an increase in titer. In most centers, the standard agglutination test (SAT) is the primary test used for serological diagnosis. Although some investigators trust the Rose-Bengal test, it is not fully validated for human diagnosis. The anti-Brucella IgM dipstick test is used to diagnose acute infection, but its sensitivity is low in infections with symptoms lasting several months. In endemic areas, >90% of patients with acute bacteremia have SAT titers of at least 1/320.

Treatment

The gold standard treatment of brucellosis in adults is the combination of intramuscular streptomycin (0.75 to 1 g per day for 14-21 days) with doxycycline (100 mg twice daily for six weeks). Clinical and observational studies have shown that the recurrence rate in patients with this treatment is 5-10%. An alternative to this treatment (recommended by the World Health Organization) is the use of rifampin (600-900 mg/day) plus doxycycline (100 mg twice daily) for six weeks.[31] Instead of streptomycin, other aminoglycosides such as netilmicin or gentamicin 5-6

mg/kg/day for at least two weeks (shorter courses have a high failure rate in adults). High doses of ofloxacin (400 mg twice daily) or ciprofloxacin (500 mg twice daily) combined with rifampin for six weeks may be an alternative to other 6-week treatment regimens in adults. Significant neurologic disorders due to Brucella require prolonged treatment (i.e., 3-6 months) with ceftriaxone added to the standard treatment regimen. Brucella endocarditis is treated with at least three drugs (an aminoglycoside, a tetracycline, and rifampin). Most experts add ceftriaxone and/or fluoroquinolone to reduce the need for valve replacement. Treatment is usually given for at least six months.

TULAREMIA

Tularemia is a zoonosis caused by Francisella Tularensis.[32] It can develop in any age, gender, and race, and almost everyone is susceptible to the disease. Tularemia is usually a disease of wild animals and survives in contaminated environments, ectoparasites, and carrier animals. Human infection is accidental and usually occurs through interaction with blood-sucking insecticides, contact with wild or domestic animals, ingesting contaminated water and food, or inhaling infected aerosols. Tularemia is characterized by pyogranulomatous pathology with mononuclear cell infiltration. Histopathologic findings are very similar to tuberculosis. However, it develops much faster in tularemia. As a facultative intracellular bacterium, F. tularensis can survive for long periods of time in both phagocytic and nonphagocytic host cells. In the acute phase of infection, focal areas of necrosis are present in the primary affected organs (skin, lymph nodes, liver, and spleen). They are initially surrounded by polymorphonuclear loci (PNL). Granulomas with epithelioid cells, lymphocytes, and multinucleated giant cells develop around the necrosis area. These areas may resemble caseating necrosis but later coalesce into an abscess.

Diagnosis

The diagnosis of tularemia is often made by agglutination testing. Microagglutination and tube agglutination tests are the most commonly used tests for detecting F. tularensis antibodies.[32] A standard tube agglutination titer of 1/160 and above is considered positive. A four-fold increase in the titer in serum samples taken 2-3 weeks later is diagnostic.

Treatment

Streptomycin, gentamicin, and quinolones can be used in treatment [33].

CAT SCRATCH DISEASE (CSD)

CSD is a self-limiting disease characterized by regional lymphadenopathy lasting weeks to months. Bartonella Henselae is the main causative gram-negative microorganism [34]. Rarely, patients with CSD develop disseminated B. Henselae infection.

Risk factor: Cat scratching or biting.

Clinical signs initially - the primary inoculation lesion - are papules, vesicles, or nodules 0.5-1 cm in size at the site of inoculation with B. henselae and persist for approximately 1-3 weeks. Adenopathy typically develops 2-3 weeks later (between 3-50 days) after scratching or biting. Unilateral solitary or regional lymphadenopathy is seen in more than 90% of cases. Their location coincides with areas of lymphatic drainage. The lymph nodes are painful, firm, mobile, and suppurative, with approximately 10% rarely erythematous. Nonsuppurative systemic symptoms such as fever, anorexia, headache, myalgia, malaise, and abdominal pain are variably present at this time. Lymphadenopathy usually resolves within three months. Histologic examination of lymph nodes in the early phase of CSD reveals follicular hyperplasia and arteriolar proliferation. Within weeks, cortical granulomas, multinucleated giant cells, neutrophilic infiltrates, and micro abscesses with a tendency to coalesce (satellite microabscesses) are observed. The granulomas are surrounded by histiocytes and peripherally by lymphocytes. Typical clinical findings and a history of cat contact suspect the diagnosis of CSD.

Diagnosis

In most cases, a lymph node biopsy or aspiration is necessary to exclude other diseases and to make a diagnosis. In such cases, polymerase chain reaction (PCR) examination of tissue samples is usually preferred. Lymph node tissue cultures are rarely positive [35]

Treatment

Most typical cases of CSD resolve without treatment. Some experts recommend treatment with azithromycin to accelerate the resolution of lymphadenopathy [36]. Antimicrobial therapy for CSD is universally recommended in immunosuppressed patients.

LYMPHOGRANULOMA VENERIUM (LGV)

It is a sexually transmitted disease caused by L1, L2, and L3 serovars of Chlamydia Trachomatis. Classically, acute LGV is characterized by a transient primary genital lesion followed by multilocular suppurative regional lymphadenopathy.[37] The primary genital lesion appears within three days to 3 weeks after exposure. It is a small, painless, vesicular, or indurated ulcer or papular lesion located on the penis in men and labia or posterior vagina in women. Acute LGV is almost always associated with systemic symptoms such as fever and leukocytosis, but systemic complications such as meningoencephalitis are rare. Nocturnal complications that develop over years if left untreated include genital elephantiasis due to lymphatic involvement, adhesions, and fistulas of the penis, urethra, and rectum.

Diagnosis

There are four different laboratory methods to confirm C. Trachomatis infection: direct microscopic examination of tissue samples to visualize typical intracytoplasmic inclusions or elementary bodies; isolation of the organism in cell cultures; immunological detection of chlamydia antigens or chlamydia genes by NAAT; detection of antibodies in serum or local secretions.[38]

Treatment

In LGV, doxycycline (2x100 mg PO) or erythromycin base (4x500 mg PO) is recommended for at least three weeks.[38]

Q FEVER

Q fever is a zoonotic infection caused by Coxiella burnetti. These organisms have a spore form that allows them to survive in harsh environmental conditions. The primary source of human infections is infected cattle and sheep. C. burnetti can also be transmitted to humans by cats, rabbits, pigeons, and dogs. [39] Chronic Q fever, almost always meaning endocarditis, is usually seen in patients with previous heart valve disease, immunosuppression, or chronic renal failure. Valvular vegetation is detected in only 12% of patients on transthoracic echography but a higher percentage on transesophageal echography. Vegetation in chronic Q fever endocarditis differs from that in bacterial endocarditis, where it appears as an endothelialized nodule on the valve. A high level of suspicion is required for correct diagnosis. Q fever should always be suspected in patients with culture-negative endocarditis.[40]

HISTOPLASMOSIS

Histoplasma capsulatum, a thermally dimorphic fungus, is the etiologic agent of histoplasmosis. When soil containing the organism is tilled, the microconidia become airborne and are transmitted to nearby people. Activities that lead to contact with high concentrations of the fungus include caving, excavation, cleaning chicken coops, demolition and renovation of old buildings, and felling of mature trees. Infection occurs after inhalation of microconidia.[41] Once microconidia reach the alveolar spaces, they are rapidly recognized and phagocytosed by alveolar macrophages. At this point, the microconidia transform into budding yeasts; this transformation is essential for the pathogenesis of histoplasmosis and depends on the presence of calcium and iron in the phagocyte. Yeasts can grow and multiply within resting macrophages. In the immunocompetent host, macrophages, lymphocytes, and epithelial cells organize and form granulomas containing the organism. These granulomas typically show fibrotic changes and calcify. Calcified mediastinal lymph nodes and hepatosplenic calcifications are often found in healthy individuals living in endemic areas. The gold standard diagnostic test for histoplasmosis is fungal culture.

Treatment

Liposomal Amphotericin B more than two weeks in case of disseminated disease, followed by itraconazole 3x 200 mg 3 days, followed by 2x200 mg ≥ 12 months. In mild cases, itraconazole 3x200 mg 3 days, followed by 2x200 mg ≥ 12 months.

Prophylaxis: CD4 T lymphocyte count < 150 cells/mm³ + living in an endemic area indicates prophylaxis and medical treatment can be adjusted as Itraconazole 200 mg/day.[42]

SARCOIDOSIS

Sarcoidosis is a systemic granulomatous disease of unknown cause. The most common populations are Scandinavians and African Americans.[43] The estimated annual incidence of sarcoidosis in Turkey is 4/100,000.[44] The most common age of onset is 20-40 years, the second most common age is over 50 years, and it is more common in the female gender. It is more common in non-smokers (approximately 75% of cases).[45]

In sarcoidosis, a cellular immune response is triggered by antigen. When the cytokines released are analyzed, it is thought to be a T-helper 1 (Th1) mediated immune response. In sarcoidosis, CD4+

Th1 cells and macrophages gather in areas where inflammation is prominent, especially in the lungs. Granulomas are formed by the cytokines secreted by these cells.[46]

The typical histopathologic lesion of sarcoidosis is dense epithelioid cell granulomas without caseating necrosis. Granulomas contain epithelioid cells, giant cells (asteroid bodies and Schumann bodies), and lymphocytes. Granulomas may disappear or progress to fibrosis.[47]

The most common organ involved in sarcoidosis is the lungs. While many patients with pulmonary sarcoidosis are asymptomatic and diagnosed incidentally with chest radiography, some patients may present with non-specific complaints such as exertional dyspnea, cough, fatigue, and chest pain.[48,49]

Physical examination findings in pulmonary sarcoidosis are not very specific. Despite radiologic prevalence, rales can be heard in up to 20% of patients. Development of clubbing is rare. Cor pulmonale may develop in very advanced cases.[50]

Radiologic staging in sarcoidosis is performed according to chest radiography:[51]

Stage 0: Normal chest radiography

Stage 1: Bilateral hilar lymphadenopathy

Stage 2: Parenchymal infiltration with bilateral hilar lymphadenopathy

Stage 3: Parenchymal infiltration only

Stage 4: Fibrosis

Extra-thoracic Involvement

Approximately one-third of patients have palpable peripheral lymph nodes. Cervical, axillary, epitrochlear, and inguinal lymph nodes are most commonly involved.[52] Skin involvement occurs in one-third of patients and is the most common extra-thoracic manifestation of sarcoidosis.[53] Erythema nodosum is the most common non-specific skin lesion. It is typically painful, erythematous, and predominantly found on the anterior aspect of the lower extremities.[54]

Ocular sarcoidosis is the second most common extra-thoracic manifestation. Reported ocular involvement ranges from 10% to 25% and is more common in blacks and women.[53,55,56] Any part of the eye can be affected; uveitis is the most common form of involvement.

Joint pain occurs in 25-39% of patients with sarcoidosis, while deforming arthritis is rare [57]. The most commonly involved joints are the knees, ankles, elbows, wrists, and small joints of the hands and feet.

Liver involvement is quite common (30% in the antemortem series and up to 80% in the postmortem series).[58] Most patients are asymptomatic, with non-specific abdominal pain, nausea, and fatigue being the most common symptoms.[59,60] The prognosis is good with spontaneous regression and rapid response to corticosteroids. [59,60]

Involvement of the nervous system in patients with sarcoidosis ranges from 3% to 10%.[53,58] Systemic manifestations of sarcoidosis are also observed in more than 90% of cases of neurosarcoidosis, especially in the lungs and intrathoracic lymph nodes. Any part of the nervous system can be affected, and multiple involvement can occur in a single patient. The most commonly involved areas are the cranial nerves, meninges, and brain parenchyma.[61]

The classical renal involvement of sarcoidosis is granulomatous interstitial nephritis, which has been observed in 20% of postmortem studies.[62,63]

Cardiac Involvement

The reported cardiac prevalence in sarcoidosis ranges from 1% to 23%.[58] Differences in the methods and criteria used to detect and diagnose cardiac sarcoidosis are probably responsible for this wide range.[54] Cardiac sarcoidosis involvement may occur in isolation without the involvement of other organs. The significant pathology here is granulomatous inflammation of the myocardium, leading to arrhythmia and cardiomyopathy.[64] The most common type of arrhythmia is atrioventricular block, accounting for about half of patients, followed by ventricular tachycardia and supraventricular arrhythmia.[65,66] Patients may be asymptomatic, especially in the early stage of the disease, or may experience palpitations, syncope, and even sudden cardiac death.[67] Heart failure due to cardiomyopathy is the first manifestation of cardiac sarcoidosis in 10-20% of patients.[65,66] Heart failure can be seen in dilated cardiomyopathy with reduced ejection fraction (EF) and restrictive cardiomyopathy with preserved EF.[64]

Diagnosis

In cases where a clinical-radiological pattern consistent with sarcoidosis is supported by histopathological detection of dense, primarily non-caseating, giant cell granulomas, a definitive diagnosis of sarcoidosis is made in the absence of any evidence of another granulomatous disease.[68] These include Lofgren's syndrome (arthritis, erythema nodosum,

Hilar Lymphadenopathy), Heerfordt syndrome (fever, parotid gland enlargement, anterior uveitis, facial paralysis), involvement of the lacrimal and parotid glands on Gallium-67 scintigraphy (panda sign) and right paratracheal and bilateral hilar involvement (lambda sign).[69]

The best biopsy site depends on the accessibility of the lesion, the safety, and the potential yield of the procedure. Biopsy specimens of superficial lesions (skin lesions other than erythema nodosum, palpable peripheral lymph nodes, minor salivary gland, or visible conjunctival nodules) should be considered before other sites. If none of these factors is present, endobronchial and transbronchial lung biopsy with flexible bronchoscopy and lymph node sampling with endobronchial ultrasonography (EBUS) should be considered[70] Due to its high diagnostic rate, transbronchial needle aspiration with EBUS has replaced mediastinoscopy to evaluate mediastinal and hilar lymph nodes[71]

Bronchoalveolar lavage revealed moderate lymphocytosis in 80% of cases (20-50%) and a CD4/CD8 ratio higher than 3.5 in 50%. These findings are used to support the diagnosis of sarcoidosis.[72]

Treatment

A personalized approach to patients seems imperative due to changing disease manifestations, significant variability in treatment response, and the wide range of treatment options.[73]

The spontaneous remission rate is 55-90% in stage I, 40-70% in stage II, and 10-20% in stage III. Spontaneous remission is not seen in stage IV. Corticosteroids (CS) are the mainstay of pharmacologic treatment of pulmonary sarcoidosis due to their potent macrophage inhibition and lymphocyte activation. They are considered first-line therapy in sarcoidosis. There is insufficient evidence on the dose and duration of treatment. Recent data and accumulated clinical experience suggest that an initial dose (20-40 mg prednisone equivalent) should be given for 1 to 3 months, followed by re-evaluation, followed by a reduction to a maintenance dose of 5-10 mg/day, which may be prolonged for up to one year. In patients with mild disease such as skin lesions, anterior uveitis, or cough, topical steroid therapy may be all that is required. Oral corticosteroids are usually used in those with systemic and symptomatic disease. Systemic therapy is indicated for cardiac and neurologic involvement, ocular involvement not responding to treatment, and hypercalcemia. In pulmonary and other extrapulmonary involvement, most physicians generally consider that progressive, symptomatic disease should be treated[74]

Cytotoxic/antimetabolite agents are also used in patients who progress despite CS or develop CS toxicity/side effects. Methotrexate is the most widely used and well-studied agent for pulmonary sarcoidosis. The usual dose is 10-25 mg orally or intramuscularly weekly. Maximum efficacy is reached 2-3 months after the start of treatment. Less commonly used agents are Azathioprine, Leflunomide, Mycophenolate, and Chloroquine/Hydroxychloroquine.[75]

Another treatment option is biologic agents. They can be used in patients who cannot tolerate antimetabolites. Tumor necrosis factor (TNF) alpha inhibitors, particularly infliximab and adalimumab, are the most commonly used.[76]

ULCERATIVE COLITIS

Ulcerative colitis (UC) is a chronic mucosal inflammation of unknown etiology that involves the colonic mucosa from the rectum to the proximal part. It is ex[77] pected between 20-40 and 55-65 ages. It is less common in smokers. The most common site of involvement is the rectum. Inflammation almost always starts from the rectum and progresses towards the cecum. Inflammation is superficial, rarely crosses the lamina propria, and does not involve the serosa. Intestinal involvement is diffuse, with no intervening intact areas.[78] Pathologically, crypt abscesses are observed in the involved areas. Post-inflammatory pseudopolyps, epithelial goblet cell loss occurs during the healing period. In the chronic period, the appearance of lead pipe (loss of haustrations, smooth muscle thickening, shortening of the colon) may occur.

Bloody diarrhea is the most common presenting complaint in ulcerative colitis.[79] Rectal bleeding, tenesmus, and mucopurulent stools are common. Systemic symptoms such as fever, fatigue, night sweats, nausea, vomiting, and arthralgia may be present. Skin, joint, eye, liver, hematologic, and extraintestinal manifestations may occur. The most common laboratory pathology is iron deficiency anemia.[80] P-ANCA is positive as an autoantibody in 50-80% of cases.[81]

Complications may include fulminant colitis, toxic megacolon, risk of colon cancer, massive hemorrhage, perforation, thromboembolism, stricture, obstruction, and perianal disease.

Diagnosis

There are no clinical and laboratory findings that make the diagnosis alone. Increased acute phase reactants, significantly elevated CRP, increased sedimentation, leukocytosis, thrombocytosis, anemia, and hypoalbuminemia may be observed. Fecal lactoferrin and especially calprotectin in stool reflects intestinal inflammation.[82]

An edematous, edematous fragile hyperemic granular mucosa that bleeds easily is typical on endoscopy. It is seen with superficial and irregular ulcers. Pseudopolyps are seen in the chronic phase. Radiologically, ulceration pseudopolyps and loss of haustrations can be seen in double contrast colon radiography.

Microscopic Features

The disease is limited to the mucosa and superficial submucosa. The deeper layers are intact except in fulminant disease. Two main histologic features of UC suggest chronicity and help to distinguish it from infectious or acute self-limiting colitis. First, the crypt structure of the colon is distorted; crypts may be cleft and reduced in number, often with a gap between the crypt base and the muscularis mucosa. Second, some patients have basal plasma cells and multiple basal lymphoid aggregates. Mucosal vascular congestion may be accompanied by edema, focal hemorrhage, and an inflammatory cell infiltrate, including neutrophils, lymphocytes, plasma cells, and macrophages. Neutrophils invade the epithelium, especially in crypts, causing cryptitis and, eventually, crypt abscesses.[83]

Treatment

5-Aminosalicylic acid [Topical (rectal) or oral sulfasalazine or mesalamine], corticosteroids, and immunosuppressants (mercaptopurine and azathioprine can be used in maintenance therapy) are used for the treatment of ulcerative colitis. Cyclosporine is effective in acute and maintenance but is used in selected cases due to toxic effects. TNF alpha antagonists, infliximab, adalimumab, and golimumab (acute and maintenance), are used in treatment.[84]

Proctocolectomy is performed in cases of toxic megacolon, perforation, non-stop bleeding, severe dysplasia on biopsy, and unresponsive to medical treatment.[85]

CROHN'S DISEASE

It is a chronic granulomatous inflammatory disease with remissions and relapses that can involve the gastrointestinal tract transmurally from the mouth to the anus. It can involve anywhere from the mouth to the anus (most commonly as ileocolitis -distal ileum and proximal colon are involved).[86] Involvement is segmental and transmural; the earliest macroscopic lesion is aphthous ulcer.[87] Dyspeptic complaints, abdominal pain, tenderness, and bloody diarrhea may occur in colon involvement. Weight loss and clubbing may be observed in patients. Systemic symptoms secondary to malabsorption are more common. Since the involvement is transmural, fistula, stricture, obstruction, and intrabdominal abscess may be observed, and colon cancer risk is increased. Erythema nodosum, peripheral arthritis, and ankylosing spondylitis are more common in Crohn's disease (CD).[88] Gallstones, osteomalacia, vitamin deficiencies, calcium oxalate stones, and obstructive uropathy are specific to CD and not expected in UC.[89] Sclerosing cholangitis and pyoderma gangrenosum are more common in UC.

Diagnosis

Increased acute phase reactants and significantly elevated CRP are observed. Fecal lactoferrin and especially calprotectin in stool reflects intestinal inflammation.[82] Laboratory abnormalities are more prominent due to small bowel involvement and malabsorption. CT and MR enterography are primarily ordered for small bowel imaging. Capsule endoscopy is superior to radiologic methods. Hyperemic and edematous mucosa, deep linear ulcers between edematous areas, and rough mucosa (paving stone appearance) can be detected in the involved segments.[90,91] In the differential diagnosis, infective agents, diverticulitis, ischemic colitis, radiation colitis, solitary rectal ulcer, NSAID-induced colitis, and drugs causing colitis (i.e., Mycophenolate mofetil and Ipilimumab) are included.

Microscopic Features

The earliest lesions are aphthous ulcerations and focal crypt abscesses. In focal crypt abscesses, scattered macrophage coagulations form noncaseating granulomas in all layers of the intestinal wall. Granulomas can occur in lymph nodes, mesentery, peritoneum, liver, and pancreas. Although granulomas are a pathognomonic feature of CD, they are rarely found in mucosal biopsies. Surgical resection reveals granulomas in about half of cases. Other histologic features of CD include the presence of submucosal or subserosal lymphoid aggregates, especially in

areas distant from the ulceration sites, macroscopic and microscopic jumping areas, and transmural inflammation characterized by fissures and sometimes fistulous tracts or local abscess formation deep into the intestinal wall.[92]

Treatment

5-Aminosalicylic acid: Topical (rectal) or oral sulfasalazine or mesalamine; limited efficacy in ileal disease, given if colon involvement is present.

Corticosteroids, Immunosuppression: Mercaptopurine and azathioprine are used in maintenance therapy, and TNF alpha antagonists (infliximab, adalimumab, certolizumab) are used in both acute and maintenance therapy.[93]

Monoclonal antibodies (anti-alpha four integrins): Natalizumab, ustekinumab, and vedolizumab are used for the treatment.

Antibiotics: Metronidazole and ciprofloxacin are preferred for suppressing active inflammation, perianal disease, and fistulizing cases.

Elemental diet: A liquid diet of amino acids and small nutrient molecules is given.

Surgery: It is performed in case of complications.

PRIMARY BILIARY CIRRHOSIS

It is an autoimmune disease characterized by progressive middle and slight intrahepatic bile duct damage.[94] The common bile ducts are not affected. Ninety percent are female and usually present clinically in middle age.

Histopathologic analysis of liver biopsies from PBS patients has shown that there are four distinct stages as the disease progresses. The earliest lesion is chronic nonsuppurative destructive cholangitis and is a necrotizing inflammatory process of the portal tracts. The middle and small bile ducts are infiltrated with lymphocytes and undergo constriction. Mild fibrosis and sometimes bile stasis may be seen. With progression, the inflammatory infiltrate is less prominent, but the number of bile ducts is reduced, and smaller bile ducts are proliferated. With increased periportal fibrosis, the fibrosis spreads and turns into bridging fibrosis. Eventually, cirrhosis may develop micronodular or macronodular.[95]

Clinical Presentation

Non-specific symptoms such as fatigue, drowsiness, and arthralgia are seen in the early period. Pruritus is the first and most crucial symptom suggestive of hepatobiliary disease. Jaundice develops months to years after pruritus.[96] Skin darkening, pruritus scars, bone pain, weight loss, fat malabsorption, and xanthomas may be seen. Hypercholesterolemia is present, but cardiovascular mortality is not increased because lipoprotein decreases. Portal hypertension and signs of cirrhosis occur in the later period. Sjogren's syndrome is the most common. CREST syndrome (Calcinosis, Reynaud, Esophageal hypomotility, Sclerodactyly, and Telangiectasia) and other autoimmune diseases may be associated.[97]

Diagnosis

Cholestasis enzymes and direct bilirubin levels are increased. Bilirubin level is the most critical determinant of prognosis. Serum Ig M level is increased [98]. AMA is 95% positive and is the most essential serologic finding.[99] USG, MRCP, and ERCP are used to differentiate from pathologies causing extrahepatic cholestasis. A definitive diagnosis is made by demonstrating small- and medium-sized bile duct damage in a liver biopsy.

Treatment

Supportive treatment: Nutritional support, vitamin D, vitamin K support, calcium replacement, and cholestyramine for itching can be given.

Ursodeoxycholic acid slows the course of the disease, reduces symptoms, is more useful in early onset, and is not curative; obeticholic acid is recommended in unresponsive cases. Liver transplantation should be performed when liver failure develops.

RHEUMATOID ARTHRITIS

Rheumatoid Arthritis (RA) is a chronic inflammatory joint disease. Although its main target is synovial tissue, it is considered a connective tissue disease because of its involvement in many systems.[100] The female-to-male ratio is 3/1, which most commonly starts in the 25-55 age range. The clinic usually begins insidiously with mild joint pain and morning stiffness accompanied by general symptoms such as fatigue, subfebrile fever, and weight loss.

Joint Findings

Symmetrical polyarticular arthritis is characterized by pain, swelling, and increased temperature in the affected joint.[101] Morning stiffness in the joint lasting longer than 30 minutes is characteristic and decreases with movement. It usually starts from the small joints of the hand (PIF and MCP) and foot (MTP). Large joints are involved later. It may involve the atlantoaxial

joint (C1-C2). The least expected joints involved in RA are DIP and intervertebral joints, except for the atlantoaxial (C1-C2) and sacroiliac joints.

Extra-articular involvement.[102]

Skin: Rheumatoid nodules, vasculitis

Eye: Keratoconjunctivitis sicca, episcleritis

Mouth: Sikka symptoms

Respiratory: Pulmonary fibrosis, pleural effusion

Heart: Pericarditis, myocarditis

Neurological: Mononeuritis, entrapment neuropathies

Liver: Elevated transaminases

Hematologic: Anemia, thrombocytosis, leukocytosis, LAP, Felty syndrome (splenomegaly + neutropenia + rheumatoid arthritis)

The presence of extra-articular findings is a poor prognostic indicator.[103] Rheumatoid nodules may develop in 20-30% of RA patients. It is the most common extra-articular finding. They usually develop in periarticular structures, extensor surfaces, and other areas subjected to mechanical compression but can be found almost anywhere, including the pleura and menisci. They are frequently located in the olecranon bursa, proximal ulna, Achilles tendon, and arch head. The nodules are of varying size and consistency and rarely cause complaints but are sometimes disrupted by trauma and may become infected. They are almost always found in individuals with positive rheumatoid factor (RF). Histologically, three regions are seen in rheumatoid nodules. The central zone contains necrotic material consisting of collagen, non-collagen fibers, and cellular debris; the middle zone contains radiating macrophages expressing HLA-DR antigens; and the outer zone contains granulation tissue.[104]

Non-specific markers of inflammation, such as erythrocyte sedimentation rate (ESR) and CRP, are associated with disease activity. RF is positive in 75% of RA patients. Anti-CCP is positive in 75-80% of RA patients, with a specificity of 95%.105 RF and/or anti-CCP positivity in RA is associated with more severe joint disease, extra-articular involvement, and poor prognosis.[105] Anti-nuclear Antibody (ANA) and Antineutrophil cytoplasmic antibodies (particularly P-ANCA) are positive in 30% of cases.

Treatment

NSAIDs, Corticosteroids, Conventional Disease-modifying anti-rheumatic drugs (DMARDs); Methotrexate, sulfasalazine, antimalarial drugs, Leflunomide, Biological DMARDs; TNF alpha inhibitors; Infliximab, Adalimumab, Golimumab, Etanercept, Certolizumab, and Anakinra, Rituximab, Abatacept, Tocilizumab, Tofacitinib are used in selected cases.[106]

WEGENER'S GRANULOMATOSIS

Wegener's granulomatosis is characterized by granulomatous upper and lower respiratory tract vasculitis with glomerulonephritis.[107] Typical histopathological findings of Wegener's granulomatosis are granuloma formation with necrotizing vasculitis of small arteries and veins.[108] In the lungs, multiple bilateral, cavitating nodular infiltrates typically occur.

Biopsy findings almost always show typical necrotizing granulomatous vasculitis. Upper respiratory tract lesions, especially those in the sinuses and nasopharynx, typically involve inflammation, necrosis, and granuloma formation. Vasculitis may accompany these findings.

The upper respiratory tract is involved in 75% of patients with Wegener's granulomatosis.[108] Patients often present with paranasal sinus pain and drainage, purulent or bloody nasal discharge. Nasal mucosal ulcers may also be presenting symptoms. Perforation of the nasal septum may occur.[109] Serous otitis media may develop due to obstruction of the eustachian tube. Subglottic tracheal stenosis due to active disease or scarring develops in approximately 16% of patients and causes severe airway obstruction.

Pulmonary involvement may present with asymptomatic infiltrates or lead to coughing, hemoptysis, dyspnea, or discomfort in the chest. Lung involvement occurs in 85-90% of patients.[110] Endobronchial obstruction and atelectasis may develop during active disease or after fibrosis scarring.

Ocular involvement occurs in 52% of patients.[111] Involvement ranges from mild conjunctivitis to dacryocystitis, episcleritis, scleritis, granulomatous sclerouveitis, ciliary vasculitis, and retro-orbital mass lesions causing proptosis.

The sensitivity of the C-ANCA test for Wegener's granulomatosis ranges from 34% to 92%, and the specificity from 88% to 100%.[112]

CHURG-STRAUSS SYNDROME

Necrotizing vasculitis of Churg-Strauss syndrome affects small and medium-sized muscular arteries, capillaries, veins, and venules.[113] The characteristic histopathological feature is a granulomatous reaction

in the tissues and even in the vessel walls. These granulomatous structures are often accompanied by eosinophilic tissue infiltration.[114] This phenomenon can occur in any organ in the body, the most commonly affected organ being the lung. The skin, cardiovascular system, kidney, peripheral nerves, and gastrointestinal tract are also commonly involved.

Although the exact pathogenesis of the disease is unknown, the strong association with asthma and the clinical and pathologic findings of eosinophilia, granulomas, and vasculitis suggest that an exaggerated immunologic phenomenon is responsible for the onset of the disease.

GIANT CELL ARTERITIS

The most commonly involved artery in giant cell arteritis is the temporal artery. In fact, most patients have a silent systemic involvement involving multiple medium and large arteries.[115]

Histopathologic examination reveals panarteritis with inflammatory mononuclear cell infiltrates with frequent giant cell structures within the vessel wall.[116] Pathophysiological findings in organs are caused by ischemia associated with the involved vessels.[117]

CHRONIC BERYLLIUM DISEASE

Beryllium is a lightweight, stretchable, hard metal with good electrical conductivity. The cooling ability of neutrons with water is vital in controlling nuclear reactions. Although beryllium causes acute pneumonitis, it is often associated with chronic granulomatous inflammation like sarcoidosis.[118]

If occupational beryllium exposure in industries such as high-tech electricity and ceramics is not specifically questioned in a patient with sarcoidosis, the relationship between occupational exposure and etiology is missed.

The evidence distinguishing chronic beryllium disease from sarcoidosis demonstrates a beryllium-specific cellular immune response (delayed hypersensitivity). The test that often provides this evidence is the Beryllium Lymphocyte Proliferation test.[119,120]

HYPERSENSITIVITY PNEUMONITIS

Hypersensitivity pneumonitis, or extrinsic allergic alveolitis, is a non-IgE-mediated hypersensitivity reaction resulting from repeated inhalation of organic dust particles or various chemical substances.[121]

Dust (arising in agriculture), bioaerosols, microorganisms (fungal, bacterial, or protozoal), and some reactive chemical species cause the disease.

The acute response after antigen inhalation is a non-specific diffuse pneumonia characterized by mononuclear cell and neutrophil infiltration in the bronchioles, alveoli, and interstitium. With repeated exposures, a subacute stage develops with lymphocyte infiltration in the bronchioles. The chronic stage develops within three weeks and is characterized by non-caseous epithelioid granulomas. In long-term exposures, progressive fibrosis and bronchiolitis obliterans may develop. In late chronic processes, fibrosis may result in honeycomb lung with histopathology similar to usual interstitial pneumonia.[122,123]

Ethical Approval

The ethical approval is not required for the reviews

Authors' Contribution

Study Conception: HK, MİK,NK; Study Design: HK, MİK,NK; Supervision: HK, MİK,NK; Data Collection and/or Processing: HK, MİK,NK; Analysis and/or Data Interpretation: HK, MİK,NK; Literature Review: HK, MİK,NK; Critical Review: HK, MİK,NK; Manuscript preparing: HK, MİK,NK.

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