Granulomatous Hepatitis

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Granuloma

- **Morphology:**
  - Nodular reaction with transformed macrophages called “epithelioid cell”.
  - Sometimes the epitheliod cells adhere to each other under IFN-gamma stimultation, and form “giant multinucleated cells”.
  - Other inflammatory cells may be found within or around the granuloma, including lymphocytes, and eosinophiles.
  - They are usually 1-2 mm and very distinct from the surrounding liver. May coalesce to form up to 40 mm nodules.
- **Incidence:** 2-10% of liver biopsies and liver autopsies.
- **Pathogenesis:** Granulomas occur from overstimulation of macrophages by IFN-gamma and IL-2 derived from T-helper lymphocytes responding to a persistently retained antigen.

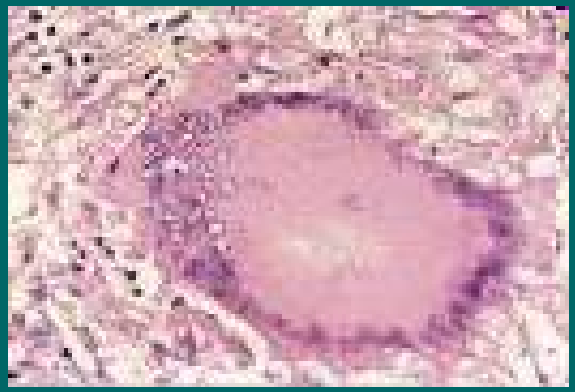
Types of Granulomas

- **Non-Necrotizing (Non-caseating):**
  - Admixture of epitheliod cells, giant cells, and lymphocytes.
  - Classic for sarcoidosis, beryllium, Crohn's, drug reaction, tuberculoid leprosy.
- **Necrotizing (Caseating):**
  - Admixture of epitheliod cells, giant cells and lymphocytes, with central necrosis. May be "palisading".
  - May co-exist with non-necrotizing granulomas.
  - Classic for Tuberculosis, Fungal infections, Rheumatoid arthritis, Wegener's & Hodgkin Disease.

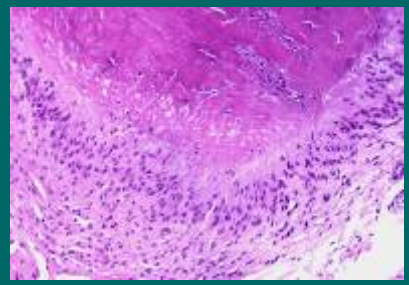
Types of Granulomas

- **Fibrin-ring:**
  - Macrophages and lymphocytes that enclose a central empty space (or lipid vacuole) often encased by a fibrin ring.
  - Classic for Q fever.
  - May be seen in CMV, EBV, Hepatitis A, MAI, leishmania, Lyme disease, Boutonnuese fever, toxoplasma, Hodgkin disease, non-Hodgkin lymphoma, and drug reaction.
- **Suppurative**:
  - Have central microabscess.
  - Often large and irregular; may be stellate.
  - Classic in cat scratch fever, lymphogranuloma, tularemia.
  - Less often in yersinia, actinomycosis, nocardiosis, fungal, or mycobacterial infection.
- **Lipogranuloma:**
  - Lipid vacuole (without fibrin ring) surrounded by macrophages or lymphocytes.
  - Classic in mineral oil, ASH, NASH, lipid-gold injections.

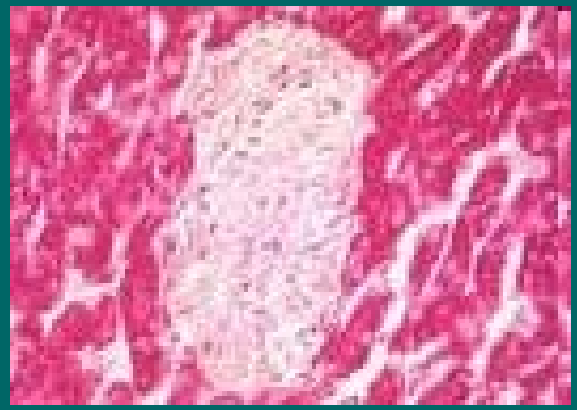
Necrotizing Granuloma



Palisading Granuloma

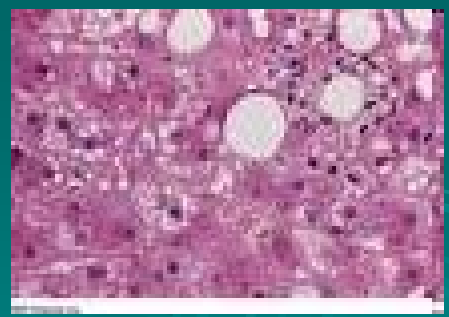


Non-Necrotizing Granuloma



Fibrin-Ring Granuloma

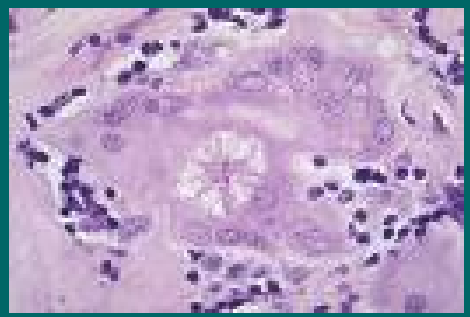
Lipogranuloma



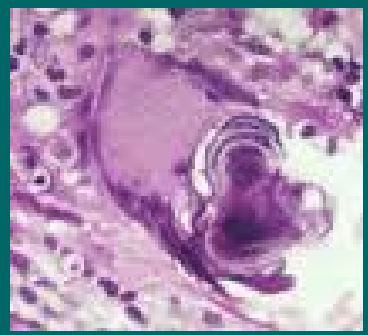
Special Findings

- a) Asteroid bodies: 5-20 mm, seen in sarcoidosis, fungal infections, silicone or teflon exposure.
- b) Schaumann bodies: 25-200 mm, oval, with Ca oxalate, Ca carbonate, Ca phosphate, or Fe; seen in sarcoidosis but not specific.
- c) Fibrosis, suggest sarcoidosis (usually periportal or portal).
- d) Associated bile duct destruction, suggest PBC (granuloma usually in portal area).
- e) Associated with eosinophiles suggests drug, or parasite (granuloma anywhere in the lobule).

Asteroid Body



Schaumann body



Special Studies in Biopsy

- Stains:
  - Ziehl-Neelsen (TB, MAC, …),
  - Silver (fungus),
  - Whartin-Starry (spirochetes, Bartonella),
  - Giemsa (parasites),
  - Birefringent bodies,
  - Red O (lipid),
  - Trichrome (fibrin).
- PCR:
  - B. henselae,
  - L. monocytogenes,
  - M. tuberculosis,
  - M. avium,
  - Y. enterocolitica,
  - Y. pseudotuberculosis,
  - CMV,
  - EBV,
  - T. gondii
  - Leishmania

Etiology of Hepatic Granulomas Several World Series

- Sarcoidosis 35%
- Tuberculosis 20%
- Undetermined 11%
- Misc. non-infectious 9% *
- PBC 5%
- Other cirrhosis 5%
- Misc. Infections 5% **
- Schistosoma 2%
- Lymphoma 2%
- Brucellosis 2%
- Drug induced 2%
- Acute viral hepatitis 1%
- Fungal infection 1%

*Pancreato/biliary disease, berylliosis, malignancy, NASH, temporal arteritis, Crohn disease, Wegener granulomatosis, erythema nodosum, eosinophilic granuloma, starch, CVID, celiac disease.

**Typhoid fever, EBV, syphilis, other bacterial infection, other viral infection, leprosy, toxoplasma, CMV, lymphogranuloma venereum, actinomycosis, influenza B, visceral larva migrans, BCG.

Clinical Manifestations of Granulomatous Hepatitis

- **Symptoms**:
  - Many patients are asymptomatic.
  - When symptomatic, they may have fever, fatigue, weight loss, abdominal pain, or malaise.
  - May have symptoms of the underlying disease.
- **Physical exam**:
  - May have hepatomegaly, splenomegaly, lymphadenomegaly.
  - May have findings of the underlying disease.

Clinical Manifestations of Granulomatous Hepatitis

- **Laboratory**:
  - Elevated alkaline phosphatase is the main finding.
  - May have some ALT & AST elevation.
  - May have high ACE and Calcium.
  - Anemia, high or low WBC count, or hypoalbuminemia reflect advanced or prolonged illness.
  - Elevated bilirrubin is less common.
- **Imaging**:
  - CT scan or ultrasound may be normal, or show hepatomegaly, diffuse non-homogeneous liver appearance, or a focal lesion.
  - Granulomas > 5 mm diameter may show as nodular lesions on MRI; sometimes they form pseudotumors.

Clinical Evolution

- In most patients is asymptomatic and non-progressive.
- Granulomas are important because they may indicate the presence of a serious disorder otherwise non-suspected.
- Frequently just a “finding” over a background of a known diagnosis (HCV, Crohn, PBC, lymphoma staging, …).
- Granulomas do not change progression of disease (but in HCV, may increase risk if IFN related sarcoidosis)
- Progressive granulomatous disease may lead to portal hypertension (PBC, sarcoidosis, Schistosomiasis, CVID with MTX therapy).
- May be part of “Fever of Unknown Origen”, in which case extensive investigations are needed to find cause and direct therapy.

Choosing the Diagnostic Work-up

Dominant Manifestation

Disease Frequency

Exposure History

Combination

Diagnostic Approach

Granuloma-type work-up

- **LIPOGRANULOMA**
  - Mineral oil
  - ASH
  - NASH
  - Gold (lipid injection)
- **SUPPURATIVE GRANULOMA**
  - Cat scratch fever,
  - Lymphogranuloma,
  - Tularemia.
  - Yersinia,
  - Actinomycosis,
  - Nocardiosis,
  - Fungal infection,
  - Mycobacterial infection.
- **FIBRING-RING**
  - Q fever
  - Boutonneuse fever
  - Leishmania
  - Toxoplasma
  - CMV
  - EBV
  - Hepatitis A
  - Lyme disease
  - MAI
  - Staphylococcus epidermidis sepsis
  - Hodgkin Disease
  - Non-Hodgkin
  - Giant cell arteritis
  - Allopurinol

Diagnostic Approach

Granuloma-type work-up

- **NECROTIZING GRANULOMA**
  - Tuberculosis
  - Hodgkin Lymphoma
  - Fungal Infection
  - Rheumatoid Arthritis
  - Wegener's
  - Churg-Strauss
  - Cat scratch fever
  - Syphilis
  - Visceral larva migrans (toxocara, capillaria)

- **PALISADING GRANULOMA**
  - Rheumatoid Arthritis
  - Churg-Strauss disease,
  - Foreign body,
  - Wegener's granulomatosis,
  - Non-TB mycobacteriosis,
  - Cat scratch disease,
  - Phaeohyphomycosis,
  - Sporotrichosis,
  - Cryptococcosis,
  - Coccidioidomycosis,
  - Syphilis
  - Visceral larva migrans (toxocara, capillaria)

Diagnostic Approach
Dominant Manifestation

- **Presence of Portal Hypertension work up:**
  - PBC
  - Sarcoidosis
  - Cirrhosis with HCV, HBV, PSC (incidental finding)
  - CVID + MTX
  - Amiodarone
- **Febrile or systemic illness work up:**
  - Sarcoidosis
  - Infection (including Whipple)
  - Infestation.
  - Lymphoma (Hodgkin, or non-Hodgkin)
  - Rheumatologic disease/ Vasculitis.
  - Renal cell Carcinoma
  - Idiopathic Granulomatous Hepatitis
  - Drug

Diagnostic Approach

Disease frequency work-up

- **Disease-frequency work-up:**
  - Sarcoidosis
  - Tuberculosis
  - PBC
  - Schistosomiasis
  - Lymphoma
  - Brucellosis
  - Fungal infection (histoplasma in Ohio valley)

Diagnostic Approach

Exposure history work-up

- **Exposure-History directed work-up:**
  - Geographic exposure (travel, birthplace)
  - Work history (farm, veterinarian, slaughter house, nuclear plant, …)
  - Leisure activity history (hunting, gardening, …)
  - Animal contact history (pets, work, farm)
  - Food preferences (unpasteurized, “organic”, uncooked)
  - Sexual contacts & practices (promiscuity, oral sex)
  - Medications (prescription, “natural”, or OTC)
  - Substance abuse (alcohol, IVDA, …)

Potential Causes by Exposure History

Environmental Exposure History

- **Outdoors, farm:**
  - Whipple
- **Contaminated water or soil:**
  - Toxocara, - Strongyloides,
  - Ancylostoma, - Necator,
  - Ascaris, - Toxoplasma,
  - Melioidosis, - Thyphoid fever,
  - Nocardiosis, - Coccidioidomycosis,
  - Aspergillosis, - Hepatitis A,
  - Schistosoma (S. America, Caribbean, Southeast Asia, China, Philippines),
  - Capillaria (Philippines, Thailand, Taiwan, Japan, Korea, Egypt, China, Indonesia, and Iran),
  - Pentastomiasis (Asia, Africa),
  - Paracoccidioidomycosis (from Mexico south to Argentina).
- **Bird or bat droppings:**
  - Histoplasma, - Chlamydia psitacii,
  - Cryptococcus

Food Exposure History

- **Unpasteurized dairy:**
  - Brucella, Listeria, Q fever.
- **Luncheon meats, undercooked chicken:**
  - Listeria
- **Undercooked/raw crayfish or crabs:**
  - Paragonimus.
- **Undercooked or raw fish:**
  - Opisthorchis (Thailand, Laos, Russia, Ukraine)
- **Unwashed vegetables:**
  - Ameba, Ascaris, Fasciola

Insect Exposure History

- **Tick bite:**
  - Tularemia,
  - Borrelia (B. burgdorferi: Lyme Disease),
  - Boutonneuse fever (Rickettsia conorii: Africa, S. Europe) .
- **Tabanid fly, mosquito:**
  - Tularemia.
- **Sand fly:**
  - Leishmania.

Tabanid fly

Ticks

Mosquito

Sand Fly

Animal Exposure History

- **Pig, goat, sheep, cattle:**
  - Brucella, Yersinia, Q fever.
- **Horse:**
  - Yersinia.
- **Rabbit, squirrel, beaver:**
  - Tularemia, Yersinia
- **Dog, cat:**
  - Toxocara
- **Kitten:**
  - Bartonella henselae.
- **Birds:**
  - Tularemia.


LES ANIMAUX DE LA FERME / FARM ANIMALS

Activity Exposure History

- **Unprotected sex:**
  - Chlamydia trachomatis, Syphilis, Hepatitis B, Hepatitis C.
- **Oral sex:**
  - Typhoid fever.
- **Poor oral hygiene:**
  - Actinomycosis.
- **IVDA:**
  - Hepatitis C, Hepatitis B, CMV, HSV, EBV.
- **Work with fluorescent lights, aerospace, nuclear reactor/weapons, electronics:**
  - Berylliosis
- **Vineyard Spraying:**
  - Copper

Substance Exposure History

Drugs

Minerals

Drug Reaction

- Aspirin
- Acetaminophen
- **Allopurinol (*)**
- Amiodarone
- Amoxicillin-Clavulanate
- **Carbamazepine (*)**
- Cephalexin
- Chlorpropamide
- Clofibrate
- Diazepam
- **Diphenylhydantoin (*)**
- Diltiazem
- Fluothane
- Glyburide
- Halothane
- HCTZ
- **Hydralazine (*)**
- INH
- Interferon (sarcoid)
- **Methyldopa (*)**

(*) Most common & better studied

Drug Reaction

- Metahydrin
- Metolazone
- Mebendazole
- Mesalamine
- Nitrofurantoin
- Norfloxacin
- Penicillin
- **Phenylbutazone (*)**
- Procainamide
- Procarbazine
- Quinine
- **Quinidine (*)**
- Pyrazinamide
- Quinidine
- Rosiglitazone
- **Sulfonamides (*)**
- Sulfasalazine
- Silicone
- Tocainide
- Thorotrast

(*) Most common & better studied

Minerals

- Beryllium
- Copper
- Silica
- Talc
- Gold (in lipid injection)
- Mineral oil

Non-Environmental Causes of Hepatic Granulomas

Malignancies & Vasculitis

- Hodgkin Disease
- Non-Hodgkin Lymphoma
- Renal cell Carcinoma
- Giant cell arteritis
- Lupus Erythematosus
- Polyarteritis nodosa
- Polymyalgia rheumatica
- Rheumatoid arthritis
- Wegener granulomatosis
- Churg-Strauss

Miscellaneous

- Sarcoidosis
- Primary Biliary Cirrhosis
- PSC
- Crohn Disease
- Ulcerative Colitis
- Jejuno-ileal bypass
- Eosinophilic granuloma of lung
- Immunodeficiency (CVID)
- Graves-Basedow hyperthyroidism
- Rheumatic Fever
- Eosinophilic gastroenteritis
- Celiac disease
- Chronic Granulomatous Disease
- Idiopathic Granulomatous Hepatitis
- NASH
- ASH
- Preservation injury
- Acute cellular rejection
- Chronic ductopenic rejection.

Diagnostic Investigations For Infections & Minerals

Mycobacterial Infections

Tuberculosis	CXR, BAL, Liver/BM culture, PCR in liver (sens 53%, specif 96%), Quantiferon/PPD, Adenosine deaminase in ascites/pleural effusion.
Atypical Mycobacteria (M. xenopi, M. genavense, M. kansasii, M. mucogenicum)	
M Avium Complex	Sputum, blood & liver culture, PCR in liver. HIV test, CD4< 50
Disseminated BCG (bladder immunotherapy)	History BCG bladder irrigation.
Leprosy L	AFB stain, geographic exposure, clinical features, anti-phenolic glycolipid-1 (PGL-1) by ELISA

Bacterial Infections

- Brucella
  - Exposure to pig/goat/cattle. Unpasteurized dairy. Blood/BM culture, agglutinin test.
- Bartonella Henselae
  - Kitten scratch. Serology. PCR in liver.
- Listeria
  - Unpasteurized milk/cheese, luncheon meats, undercooked chicken. Blood/CNS fluid culture. PCR in liver.
- Tularemia
  - Ticks, tabanid fly, mosquito. Rabbit, squirrel, birds, beaver, …Blood culture, serology.
- Yersinia enterocolitica
  - Pig, rabbit, sheep, cattle, horse…Blood/stool culture. Agglutinin test. PCR in liver.
- Melioidosis
  - Wound contaminated with water or soil. Blood, skin Bx, liver Bx culture. PCR in liver.
- Chlamydia trachomatis
  - Unprotected sex. Serovar L1, L2, L3 give LGV. PCR in urine. Serology (acute + conv)
- Chlamydia psittaci
  - Aerosol of soil with bird droppings. Blood & liver culture. Serology.
- Trophirella whippleii
  - Middle age with outdoors work/activity. Small bowel Bx (8+ in distal D or J) + PCR
- Typhoid fever
  - Contaminated food/water, oral sex. Blood/BM/stool culture, serology.

Bacterial Infections

Borrelia (Lyme Disease)	Ixodes tick bite. Serology, serum PCR
Actinomycosis	Poor oral hygiene. Liver Bx culture
Nocardiosis	Contaminated soil. Liver Bx culture
Botryomycosis (bacterial pseudomycosis) Staph aureus & Pseudomona	Culture
Propionibacterium	Skin flora. Culture.

Rickettsial, Spirochetal, & Viral Infections

Q fever	Sheep, cattle, goats, unpasteurized dairy. Serology. PCR Coxiella burnetii in liver.
Boutonneuse fever	Tick bite. Southern Europe & Africa. Serology (Rickettsia conorii)
Secondary Syphillis	Unprotected sex, promiscuity. VDRL, skin lesion,
CMV	Ubiquitous. PCR blood & liver
EBV	Ubiquitous. PCR blood/liver, serology
HSV	Ubiquitous. PCR blood & liver
V-Z virus	Human respiratory secretions. Bx culture, serum PCR
Influenza B ?	Seasonal. Nasal swab for culture or rapid test.
Hepatitis A	Serology: anti-HA IgM
Hepatitis B	Serology, HBV-DNA
Hepatitis C	Serology, HCV-RNA

Fungal Infections

- Histoplasmosis
  - Soil with bird/bat droppings. Bx/blood (isolator) culture, urine/serum Ag, comp. fixation, immunodifusion
- Blastomycosis
  - Warm, moist soil. Bx culture
- Coccidioidomycosis
  - Soil. Bx culture, complement fixation
- Cryptococcosis
  - Soil with bird droppings. Bx culture, Ag in serum/CSF
- Trichosporonosis
  - Soil, water, plants, stool. Urine/blood culture.
- Systemic candidiasis
  - Ubiquitous. Bx culture, blood culture.
- Aspergillosis
  - Decaying vegetation, soil, water. Bx culture, BAL, serology.
- Mucormycosis
  - Environment. Bx study & culture.
- Paracoccidioidomycosis
  - From Mexico south to Argentina. Soil?. Areas with coffee and tobacco. Bx culture, complement fixation, immunodifusion.

Parasitic Infestations

Schistosomiasis (Bilharziasis)	Infested water. S. America, Caribbean, Southeast Asia, China, Philippines. Stool/urine O&P. Rectal Bx. Serology.
Visceral larva migrans (Toxocariasis)	Dogs, cats, soil. Eosinophilia. Serology (ELISA).
Strongyloidiasis	South USA, Worldwide. Barefoot in contaminated soil. Stool O&P. Larvae in tissue.
Ancylostomiasis	Worldwide. Barefoot in contaminated soil. Unwashed vegetables. Stool O&P.
Necator	Worldwide. Barefoot in contaminated soil. Unwashed vegetables. Stool O&P.

Parasitic Infestations

- Ascariasis
- Capillariasis
- Enterobiasis
- Toxoplasmosis
- Leishmaniasis (visceral & viscerotropic)

- Worldwide. Contaminated soil or unwashed vegetables. Stool O&P.
- Ingestion of contaminated food, water or soil. Liver Bx with C. hepatica eggs (O&P not useful)
- Hand-to-mouth. Cellophane tape test (Graham test)
- Worldwide. Contaminated water, food, soil. Serology. Tissue PCR.
- Sandfly bite. Spleen/liver/BM culture. Serology. PCR in tissue.

Parasitic Infestations

Amebiasis	Worldwide. South USA. Contaminated water or vegetables. MSM. Stool O&P. Serology.
Giardiasis	Worldwide. Fecal-oral. Contaminated water or food. Stool O&P/giardia Ag.
Pentastomiasis (Linguatula serrata)	Asia & Africa. Ingestion of contaminated water with eggs. Bx exam.
Fasciolasis	Worldwide. Contaminated watercress. Stool O&P (low sensitivity). ELISA.
Paragonimiasis	Far East, West Africa, Central & South America. Undercooked crayfish/crabs. O&P sputum & stool.
Opisthorchiasis	Thailand, Laos, Russia, Ukraine. Undercooked fish. O&P in duodenal aspirate/stool.

Minerals

- Beryllium
  - Fluorescents, aerospace, nuclear reactors/weapons, electronics. Beryllium lymphocyte transformation test. Tissue analysis.
- Copper
  - Vineyard spraying. Copper containers.
- Silica
  - Labrador lung.
- Talc
  - Talc (Mg silicate). IVDA of tablets. Polarized microscopy (birefringent).
- Gold (in lipid injection)
  - Parenteral gold.
- Mineral oil
  - Oil laxative, “waxed” fruits.

Some Specific Causes

Sarcoidosis

- Signs and Symptoms:
  - Fever, pulmonary infiltrates, dry cough, lymphadenomegaly, weight loss, papular skin rash, uveitis.
  - Rare jaundice.
  - Hepato/ Splenomegaly in 5-10%.
- Pathology:
  - Almost all patients have liver granulomas.
- Laboratory:
  - Very high alk phosph.
  - ACE is elevated in 50-85% (non-specific).
  - May have hypercalcemia or hyperglobulinemia.
- Rare portal hypertension
  - pre-sinusoidal from granulomas, or
  - sinusoidal from fibrotic “healing” of granulomas.

Sarcoidosis

- Cirrhosis is extremely rare.
- Granulomas may cause venous stasis leading to Budd-Chiari S.
- Patients may have PBC-like cholestasis, or “vanishing bile-duct syndrome”.
- Rarely may have PSC-like periductal fibrosis.
- Treatment:
  - Only when with progressive symptoms (Wt loss, fever) and/or portal HTN.
  - Prednisone +/- Azathioprine. Anti-TNF therapy.

Tuberculosis

- Liver granulomas in:
  - 25% of pure pulmonary TB,
  - 71% of pulmonary + other organ TB,
  - 94% of miliary TB (caseating in 52%).
- Only 10% of livers with TB granulomas stain AFB(+), or grow TB in culture.
- TB liver granulomas are PCR (+) in 53 %, with specificity of 96% (PPV = 90%, NPV = 76%).
- Most patients will be PPD or Quantiferon (+); false negatives due to anergy are more common in miliary TB.
- Patients may have tuberculoma that can cause cholangitis if it ruptures in bile duct.
- Liver Bx is superior to BM Bx for diagnosis of TB (Liver 94% vs BM 53% in miliary TB)

Schistosomiasis

- 200 million infested worldwide;
  - 400000 in USA.
- Adult worm lives in mesentery veins or peri-vesical veins.
  - embolizes eggs into liver, intestine, and/or bladder.
  - eggs cause granulomas + “pipe-stem” fibrosis of Symmers following portal veins trayectory.
- Acute infection (Katayama fever):
  - occurs 4-10 wks after infestation.
  - gives fever, chills, cough, diarrhea, arthralgia, malaise, hepato-splenomegaly and eosinophilia.
- Chronic infection causes portal hypertension.

Brucellosis

- Signs & Symptoms:
  - Intermittent episodes of fever, profuse sweats, fronto-occipital headache, musculoskeletal pain (back pain), chest and abdomen pain, malaise, anorexia, and hepato-splenomegaly.
  - Patient often feels well between episodes.
- History of contact with goats, pigs, cattle
  - aerosolized, or
  - contact with wound, or
  - ingestion of unpasteurized dairy.

Q fever

- Contact with goats, sheep, or cattle.
  - Most commonly by aerosolized rickettsia (Coxiella burnetii) during “lambing”.
  - Also by tick-bite, or ingestion of unpasteurized dairy.
- Incubation 2-3 weeks.
- Sign $ Symptoms:
  - High fever, malaise, bi-frontal headache, and pneumonia.
  - Hepatomegaly in 65%.
  - May cause endocarditis.
- Elevated liver related enzymes in 11-65%.

Cat-scratch Disease

- Contact with kittens.
- Signs & Symptoms:
  - Lymphadenomegaly, malaise, osteomuscular pain, abdominal pain.
  - May have fever and/or cholestasis.
  - May cause “pseudotumor cerebri”.
  - In immunocompromised patient may cause bacillary angiomatosis/ peliosis hepatis.
  - Bacillary angiomatosis may cause pseudotumors of liver and spleen.

Lymphoma

- Both, Hodgkin & Non-Hodgkin.
- More than 50% of staging liver biopsies show granulomas.
- Presence of granulomas does not indicate liver involvement by the lymphoma.
- Patients with Hodgkin disease and granulomas have a stronger immune system, and a more favorable course.

Hepatitis C

- 5% of liver biopsies with HCV have granulomas.
- Does not cause cholestasis.
- Sometimes they are present before therapy, and other times they develop after interferon therapy.
- Patients may develop interferon-induced sarcoidosis, which often (but not always) resolves with discontinuation of therapy. Rarely needs steroid therapy.

Atypical Mycobacteria & BCG

- Atypical Mycobacteria
  - Immunocompetent host: Well formed granulomas; AFB stain rarely (+).
  - Immunocompromised host: Poorly formed granulomas with large amount of AFB(+) organisms.
- BCG:
  - Dissemination of BCG instilled in bladder as cancer treatment.
  - Fever, hypotension, weight loss, elevated liver enzymes.
  - Rarely recovered in culture, or seen in AFB stein.
  - Treatment: 6 months Rifampin + INH +/- steroids.

Drug Induced

- Requirements for diagnosis:
  - there should not be other apparent cause,
  - symptoms leading to liver biopsy should have a close temporal relation to use of the drug,
  - symptoms and liver enzyme abnormalities should resolve with drug discontinuation.
- Rechallenge is not required and may be dangerous.
- Granulomas may be associated to triaditis or lobular hepatitis; eosinophiles may or may not be present.
- Patients may have fever, arthralgia, skin rash, lymphadenomegaly, and/or peripheral blood eosinophilia.
- Hepatomegaly and jaundice may also be present.
- Jaundice is a marker of severity.

Idiopathic Granulomatous Hepatitis

- Diagnosis of exclusion after full work-up (in case of symptomatic disease).
- In many patients granulomas are an incidental finding without clinical relevance.
- Patient may have recurrent fever, fatigue, weight loss. They have variable cholestasis and may have severe pruritus.
- Treatment:
  - If PPD/Quantiferon (+) or anergic, empirical anti-TB therapy is reasonable.
  - Prednisone +/- MTX (or Azathioprine ?) is helpful, but close observation is needed in case of “unmasking” of TB or other infection.