Liver granulomatous lesions

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Histological classification of benign liver lesions

Epithelial lesions:

- Hepatocytes:
  - Hepatocellular adenoma
  - Focal nodular hyperplasia
  - Nodular regenerative hyperplasia
  - Focal fatty change
- Biliary cells:
  - Bile duct adenoma
  - Biliary hamartoma (von Meyenburg complex)

Nonepithelial lesions:

- Mesenchymal:
  - Hemangioma
  - Angiomyolipoma
  - Lipoma
  - Myolipoma
- Heterotopia:
  - Adrenal, pancreatic, or spleen tissue
- Others:
  - Peliosis hepatis
  - Inflammatory pseudotumor

. Imaging features of benign liver lesions [1–12]

Entity/imaging modality	Hemangioma	Focal nodular hyperplasia	Hepatocellular adenoma (HCA)
Ultrasound ± contrast enhancement	Homogenous, hyperechoic, sharp rim Atypical: peripheral and globular enhancement followed by central enhancement in delayed phases Absence of halo sign Sclerosing hemangiomas: very slow filling and calcified or hyalinized hemangiomas	Slightly hypo-/isoechoic Very rarely: hyperechoic Strong and homogeneous enhancement (arterial phase) Color Doppler: central arteries have a spoke wheel pattern [4, 5]	Arterial phase: homogeneous contrast enhancement, rapid complete centripetal filling Early portal venous phase: isoechoic
Computed tomography	Inhomogeneous peripheral nodular enhancement isoattenuating to the aorta, progressive centripetal contrast filling	Central vascular supply Arterial phase: homogenous hyperdense Portal phase: similar to adjacent liver [6–8]	Clear margins with peripheral enhancement Homogenous > heterogenous Steatotic: hypodense, Hemorrhagic: hyperdense
Magnetic resonance imaging	*T1:* hypointense *T2:* hyperintense [3]	*T1:* hypointense *T2* Arterial phase: strongly hyperintense, homogenous Portal venous phase: isointense to the liver The central element is hyperintense on T2 and enhances on delayed-phase imaging using extracellular contrast agents [9, 10]	*Subtypes:* (1) HNF1α-inactivated HCA: diffuse and homogeneous signal dropout on chemical shift T1-weighted sequences (2) Inflammatory HCAs: Telangiectatic features: strong hyperintense signal on T2-weighted images Persistent enhancement on delayed phase (extracellular contrast agent) (3) β-Catenin mutations in exon 3: No specific features (4) β-Catenin mutations in exons 7–8 No specific features (5) Unclassified No specific features [11, 12]

. Molecular classification of hepatocellular adenoma with information about frequency, risk factors, epidemiology, and symptoms/complications

Classes 2007 [58]	Classes 2017 [52]	Frequency, %	Risk factors	Epidemiology	Symptoms/ complications
HNF1A inactivated	HNF1A inactivated	40–50	Oral contraception	Female, liver adenomatosis	
β-Catenin activated	β-Catenin exons 7/8	3	Oral contraception, high alcohol consumption, obesity	Young age, solitary tumor	
	β-Catenin exon 3	7	Androgen, liver vascular disease	Male, young age, solitary tumor	Malignant transformation
Inflammatory	Inflammatory (mixed forms with β-catenin subtypes)	30–35	Oral contraception	Older age, inflammatory syndrome	Elevated GGT and ALP
Unclassified	Sonic hedgehog Unclassified	4 7	Oral contraception, obesity –	– –	Bleeding

HNF1A, hepatocyte nuclear factor 1α.

Occurrence of pediatric benign and malignant multifocal liver tumors by age

	Benign	Malignant
<2 years	Infantile hemangioma	Hepatoblastoma Metastatic disease
2–5 years	Adenoma[a]	Hepatoblastoma Metastatic disease Lymphoma
6–10 years	Adenoma[a] Focal nodular hyperplasia[b]	Hepatocellular carcinoma[a] Metastatic disease Lymphoma
11–18 years	Adenoma Focal nodular hyperplasia[b]	Hepatocellular carcinoma Metastatic disease Lymphoma Epithelioid hemangioendothelioma Other rare neoplasms

[a]Usually associated with underlying chronic liver disease in this age group.
[b]Commonly associated with a history of previous abdominal malignancy in this age group, such as Wilms tumor.

Clinical Classification of Liver Mass Lesions

A. Benign Mass Lesions for which No Treatment is Needed
Hepatic Hemangioma
Focal Nodular Hyperplasia (FNH)
Benign Liver Cyst
Focal Fat or Focal Fat Sparing
B. Benign Mass Lesions for which Treatment or Follow Up is Required
Hepatic Adenoma and Adenomatosis
Biliary Cystadenoma
Hepatic Abscess
Echinococcal Cysts
Granulomatous Inflammation
Inflammatory Pseudotumor of the Liver
C. Malignant Mass Lesions for which Treatment is Required if Feasible
Hepatocellular Carcinoma (HCC)
Cholangiocarcinoma
Liver Metastases from Other Primary Sites
Biliary Cystadenocarcinoma
Hepatic Angiosarcoma
Lymphoma

Three Clinical Categories of Hepatic Vascular Malformations*

Type of Malformation	Clinical Presentation	GLUT1 Reactivity	Pathologic Features	Outcome
Multifocal	Patients are usually asymptomatic, but some have CHF; manifests in first few months of life	GLUT1 positive	Small with no central necrosis	Proliferation followed by involution
Focal	Patients are usually symptomatic and may have CHF; manifests in perinatal period	GLUT1 negative	Large with central necrosis, hemorrhage, or fibrosis	Involute by age 12–14 months
Diffuse	Manifests with mass effect; patients may develop abdominal compartment syndrome or severe hypothyroidism; no CHF	Not yet established	Liver enlarged and replaced by masses	Complicated clinical course

Source.—Reference 5.

*As proposed by two large North American referral centers for vascular anomalies. The malformations differ in clinical presentation, pathologic appearance, and prognosis.

Clinical differential diagnosis of the most common liver masses

	Cirrhotic liver	Common lesions	Non-cirrhotic liver	Common lesions
Malignant mass	Hepatocellular carcinoma	a,d	Metastasis	a,b
	Cholangiocarcinoma		Well differentiated HCC	
	High grade dysplastic nodule		Fibro lamellar HCC	a,b,c,g
	Lymphoma		Cholangiocarcinoma	
	Metastasis (exceptional)		Hemangio-Endothelioma	g
			Lymphoma	
			Melanoma	
			Neuroendocrine tumor	a
			Sarcoma (angiosarcoma,leiomyosarcoma)	g
Benign mass	Low grade dysplasia	d	Hemangioma	b
	Focal fatty liver		Focal nodular hyperplasia (FNH)	a,b
	Hemangioma		Hepatic adenoma (HA)	a,b
	Hepatic adenoma	g	Nodular regenerative hyperplasia	b,f
			Partial nodular transformation	e,f
			Focal fatty infiltration	c,e
			Bile duct adenoma	

a: Hyper vascular liver tumor; b: Tumors that are extremely rare in cirrhosis but relatively frequent in healthy normal liver; c: Tumors frequent in the left lobe; d: Mainly in cirrhosis; e: Equally found in cirrhotic and non cirrhotic; f: Clinically mimics cirrhosis; g: Extremely rare tumors.

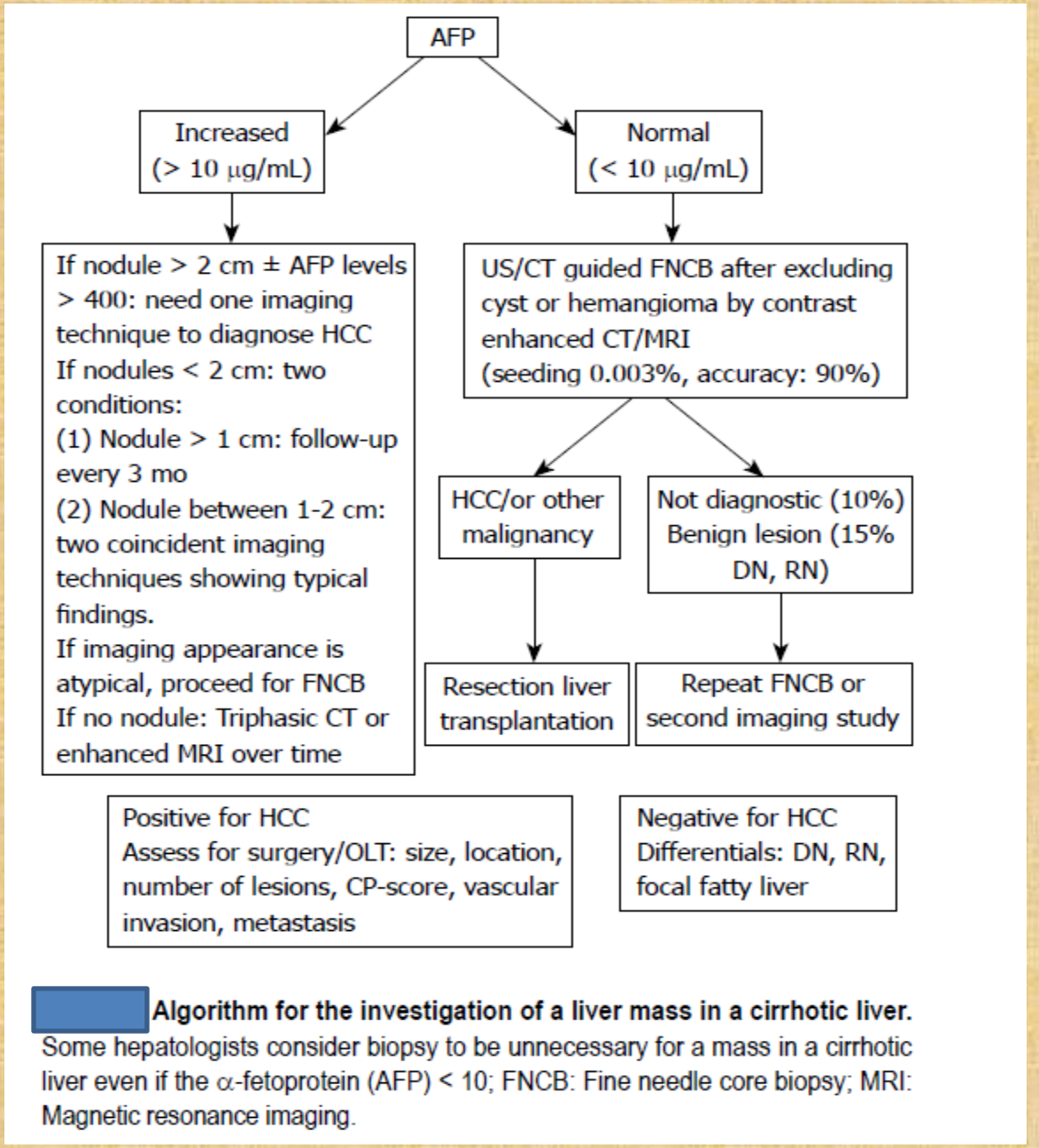
Accuracy and key features of imaging techniques in the diagnosis of most common liver masses

	US-US doppler, contrast ultrasound	Triphasic CT	MRI	PET SCAN	CT-angiography
Hemangioma (1-10 cm)	++ Hyperechoic Doppler: low flow, low index, absence of spectral broadening	+++ Peripheral puddles, fill in from periphery, enhancement on delayed scan	++++ Peripheral enhancement centripetal progression Hyperintense on T2, hypo intense on T1 SS > 95%, SP 95%	No uptake	+++ Cotton wool pooling of contrast, normal vessels without AV shunt, persistent enhancement
Focal fatty liver	+ Hyper echoic, no mass effect, no vessel displacement	++ Sharp interface Low density (< 40 u)	+++	No uptake	Normal finding
FNH (< 3 cm)	+ Homogenous iso, hypo, or hyper echoic, central hyper echoic area Central arterial signal Doppler: high flow, spectral broadening	++ Homogeneous enhance strongly with hepatic arterial phase Isodense with liver; Central low density scar	++++ Hyper vascular +Gd Isodense T1 Hyper intense scar T2 SS > 95%; SP > 95%	No uptake	+++ Hyper vascular 70% centrifugal supply
Adenoma (5-10 cm)	+ Heterogeneous Hyper echoic If haemorrhage: anechoic center In doppler: variable flow, spectral broadening	++ Homogenous > Heterogeneous, Peripheral feeders filling in from periphery	++ Capsule, Hyper intense in T1 (intra lesional fat)	No uptake uptake if degenera-tion to HCC	++ Hyper vascular Large peripheral Vessel Central scar if haemorrhage
HCC	+ Hypo or hyper echoic Doppler: hyper vascular Doppler: index and flow high, spectral broadening	+++ Hyper vascular, often irregular borders Heterogeneous > Homogeneous abnormal internal vessel Hallmark is venous washout SS 52%-54%	+++ Hyper vascular Poor different: Hypo intense T-1, Hyper intense T2 Well different: Hyper intense T-1, Iso intense T-2 SS 53%-78%	+ Increased uptake, but many HCCs show no uptake at PET	++++ Hyper vascular Av shunting Angiogenesis
Cholangio-carcinoma	Bile duct dilatation if major ducts are involved. Intra-hepatic CCC: no bile dilatation	Hypo dense lesion. Delayed enhancement	Hypo intense T1 Hyper intense T2 MRCP is useful	Uptake ++ SS 93%	Hypervascular
Metastasis	+[1] SS 40%-70% hypo to hyper echoic; doppler; low index and flow; presence of spectral broadening	+++ SS 49%-74 % complete ring enhancement	+++ SS 68%-90 % Low intensity T-1 High intensity T-2	+++++ SS 90%-100%	++++ SS 88%-95% hyper vascular

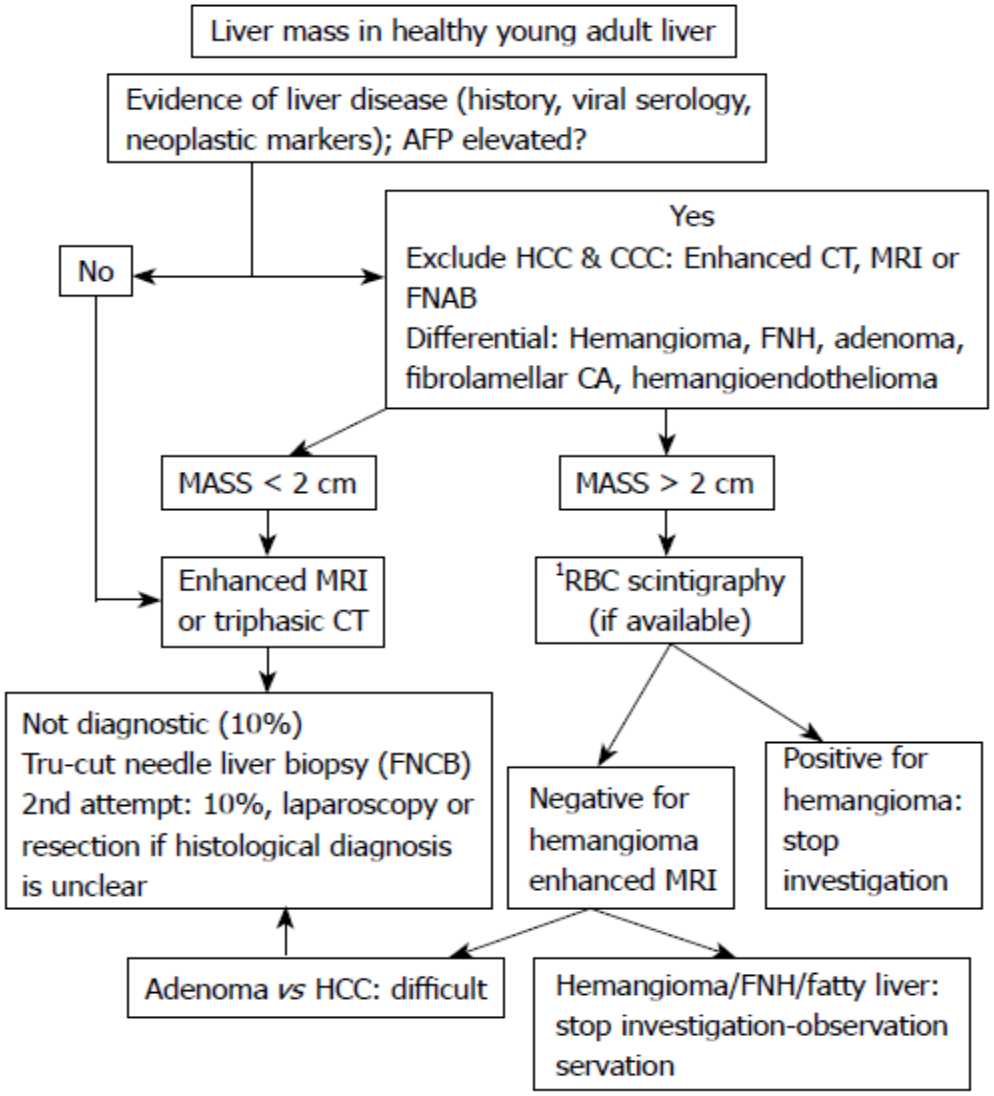
[1]Intraoperative ultrasound, contrast ultrasound and EUS are highly sensitive to detect liver mass; +: Degree of accuracy; SS: Sensitivity; SP: Specificity; MRI: Magnetic resonance imaging; CT: Computed tomography; HCC: Hepatocellular carcinoma.

Immunohistochemical staining in the evaluation of hepatic tumors

Tumor	Recommended immunostaining
HCC	Polyclonal CEA
	Cytokeratin 8/18 pair (+/+ staining)
	Cytokeratin 7/20 pair(-/- staining)
	Hep Par 1, AFP
Cholangiocarcinoma	Cytokeratin 7/19 pair (+/+ staining)
	Cytokeratin 7/20 pair (+/- staining)
	B-HCG, CEA, Mucin-1
Epithelioid	CD34
hemangioendothelioma	CD31
	Factor VIII
Angiomyolipoma	HMB-45, smooth muscle actin
Metastatic carcinoma	
Neuroendocrine	Chromagin, synaptophysin, neural enolase
Pancreas	Cytokeratin 7/20 pair (+/+ staining)
Colorectal	Cytokeratin 7/20 pair(-/+ staining)
Breast	Cytokeratin 7/20 pair (+/- staining)
Lung	Cytokeratin 7/20 pair (+/- staining)



Algorithm for the investigation of a liver mass in a cirrhotic liver. Some hepatologists consider biopsy to be unnecessary for a mass in a cirrhotic liver even if the α-fetoprotein (AFP) < 10; FNCB: Fine needle core biopsy; MRI: Magnetic resonance imaging.

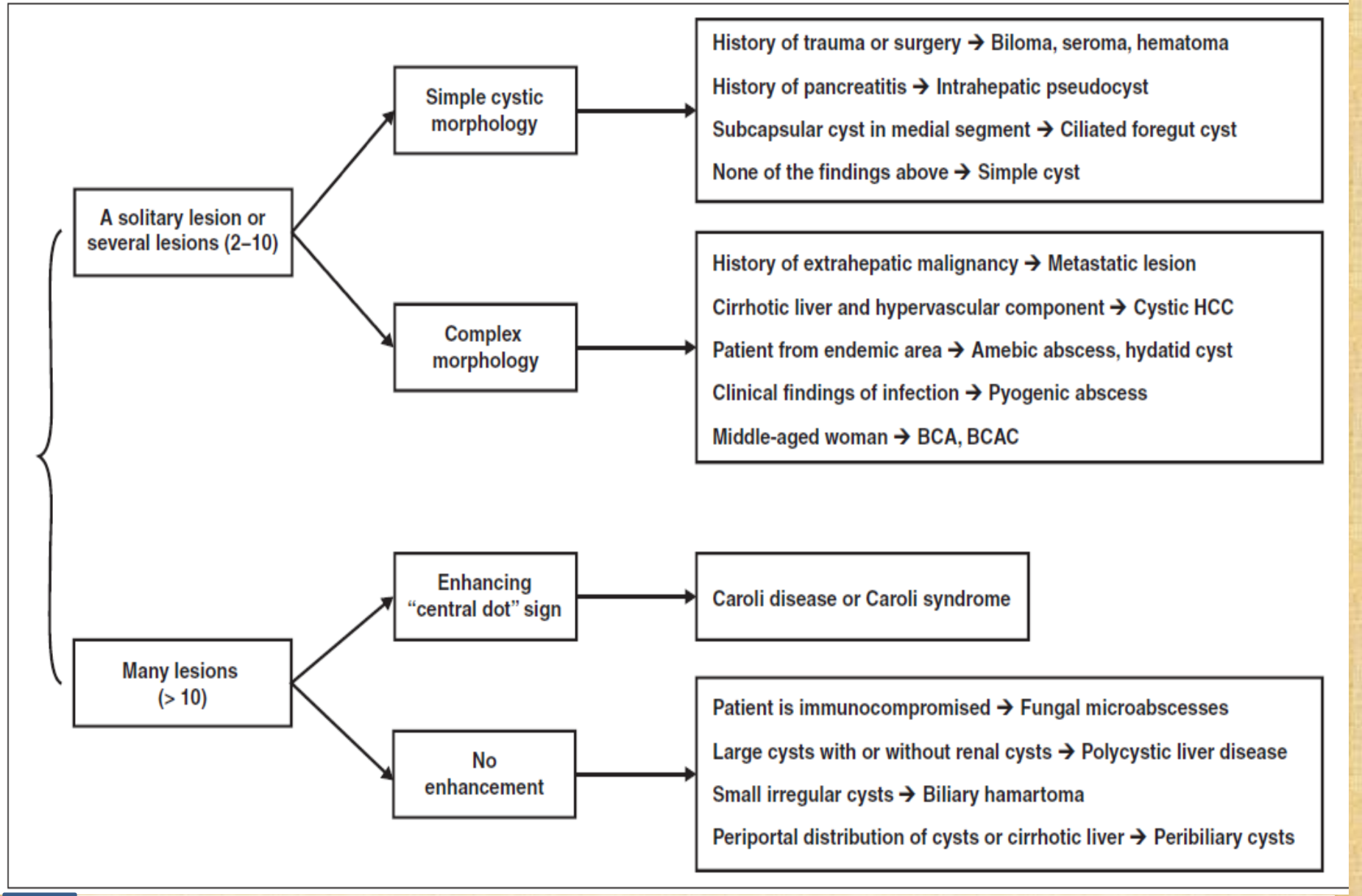


Algorithm for the management of a liver mass in a non-cirrhotic liver. [1]Most centers do not use RBC scintigraphy to diagnose hemangioma due to their use of cross sectional imaging such as contrast enhanced ultrasonography (US)/CT/MRI.

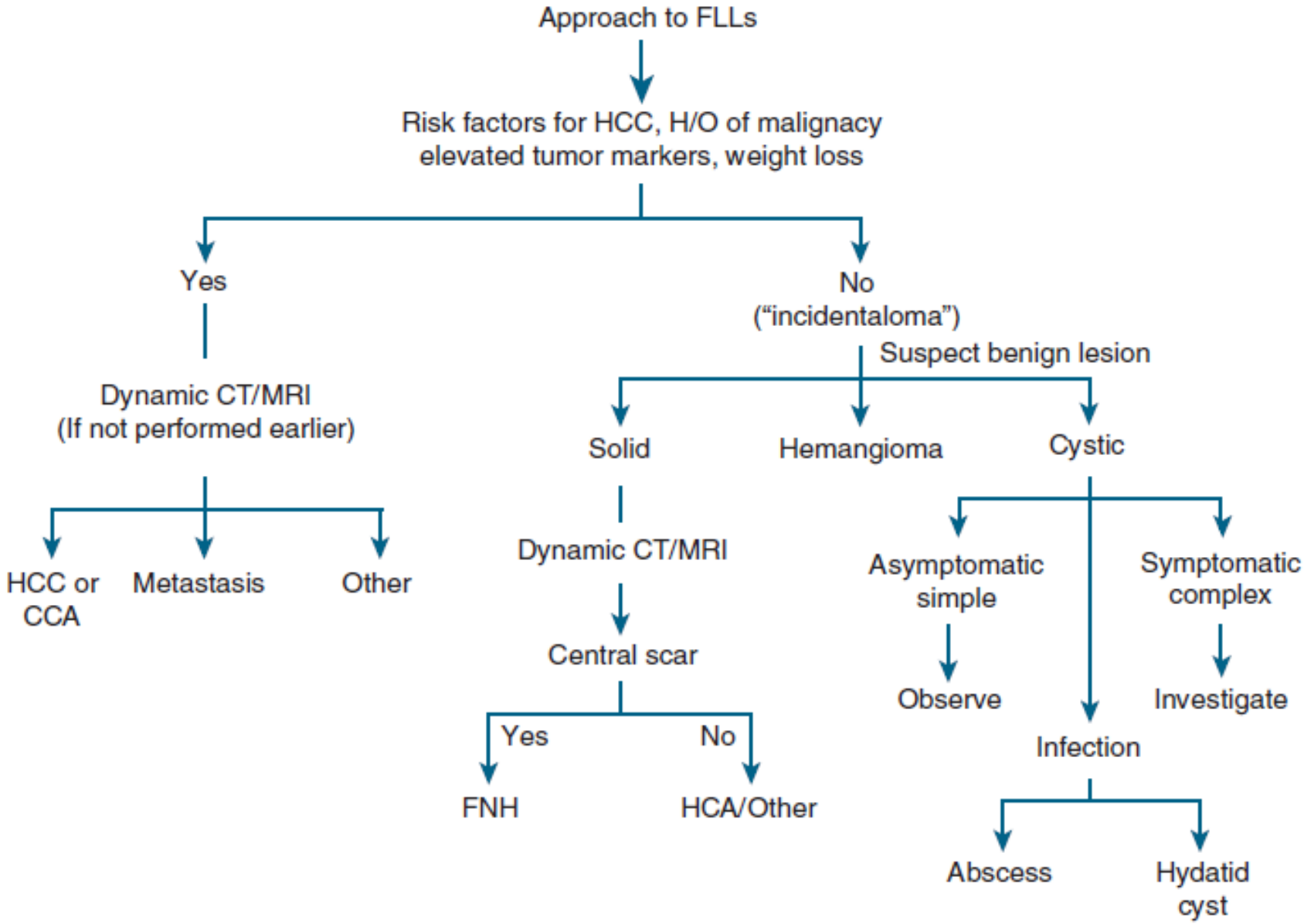
: Summary and Key Imaging and Clinical Findings of Cystic Hepatic Lesions

Lesion	Key Imaging Findings	Key Clinical Data
Developmental		
Simple cyst	Solitary cyst or multiple cysts	
Biliary hamartoma	Multiple irregular lesions	
	May have enhancing component	
Caroli disease	Multiple lesions	
	Enhancing "central dot" sign	
	Communicating with biliary tree	
Polycystic liver disease	Multiple large cysts	History of polycystic renal disease
	Usually associated with renal cysts	
Ciliated foregut duplication cyst	Classic subcapsular location in medial segment	
Inflammatory		
Pyogenic abscess	Complex cyst with enhancing rim	Clinical and laboratory findings of infection
Amebic abscess	Complex cyst with "double-target" appearance	Patient is from endemic areas
Hydatid cyst	Complex cyst with peripheral daughter cysts	Patient is from endemic areas
Fungal microabscess	Innumerable small cysts	Patient is immunocompromised
	Splenic and renal lesions may be present	
Intrahepatic pseudocyst	Findings of pancreatitis	Clinical and laboratory findings of pancreatitis
	Pseudocysts may be present in lesser sac	
Neoplastic		
Biliary cystadenoma and cystadenocarcinoma	Large complex cystic lesions with enhancing septations	Absence of infection or known metastatic disease
Cystic HCC	Complex lesion	Liver cirrhosis and increased α-fetoprotein level
	Hypervascular component with washout on portal venous phase	
Cystic metastasis	Multiple complex cystic lesions with enhancing component	History of malignancy
Undifferentiated embryonal carcinoma	Large complex cystic lesion on CT and MRI	Usually seen in adolescents
	Solid appearance on ultrasound	
Trauma-related		
Biloma	Large simple cyst with or without an enhancing pseudocapsule	History of trauma, surgery, or intervention
Seroma and hematoma	Cyst with variable density and intensity	History of trauma, surgery, or intervention
	No enhancement	

Note—HCC = hepatocellular carcinoma.



Simplified algorithm for identifying and differentiating cystic hepatic lesions. HCC = hepatocellular carcinoma, BCA = biliary cystadenoma, BCAC = biliary cystadenocarcinoma.


Approach to FLLs
Risk factors for HCC, H/O of malignacy
elevated tumor markers, weight loss
Yes
No
("incidentaloma")
Suspect benign lesion
Dynamic CT/MRI
(If not performed earlier)
Solid
Hemangioma
Cystic
HCC or
CCA
Metastasis
Other
Dynamic CT/MRI
Asymptomatic
simple
Symptomatic
complex
Central scar
Observe
Investigate
Yes
No
Infection
FNH
HCA/Other
Abscess
Hydatid
cyst

Morphologic Patterns of Liver Granulomas and Their Major Etiologic Associations

	Epithelioid	Suppurative	Microgranuloma	Lipogranuloma	Foamy	Fibrin-ring
Infectious	Tuberculosis, fungal infections, brucellosis, schistosomiasis	*Candida* infection, actinomycosis, nocardia infection	*Listeria*, other (rare)	—	*Mycobacterium avium-intracellulare* infection, leprosy, Whipple disease	Q-fever, rarely other infections (viral, salmonella)
Noninfectious	Primary biliary cholangitis, sarcoidosis, foreign body reaction, drug reaction	Chronic granulomatous disease	Nonspecific reaction to liver injury or systemic disease	Fatty liver disease, mineral oil	—	Drug reaction

Adapted from Lamps LW. Hepatic granulomas: a review with emphasis on infectious causes. *Arch Pathol Lab Med*. 2015;139:867–875.

Granuloma types and characteristics.

Granuloma types	Granuloma characteristics
Foreign body	Internal particulate material: mineral oil, starch, silicone
Lipogranuloma	Vacuoles of triglycerides
Epithelioid	Activated macrophages that can secrete cytokines and aggregate to form giant cells, or Langhans cells. Fibrin rings may form due to fibrin deposition
Lymphohistiocytic	Macrophage and lymphocyte accumulation

Geographic Variation in the Etiology of Hepatic Granulomas

	Saudi Arabia 1990[4]	Turkey 2001[8]	Scotland 2003[7]	Greece 2007[6]	Germany 2008[5]	Iran 2011[9]	Turkey 2014[10]
Number of cases	59	74	63	68	442	72	35
Incidence of granulomas (%)	14.6	1.6	3.8	3.7	3.6	2.3	1.31
Tuberculosis (%)	34	20	9	1.5	—	51.4	6
Schistosomiasis (%)	54	—	—	1.5	—	—	—
Hepatitis C (%)	—	1.3	9.5	4.4	—	4.2	6
Other infections (%)	8	31	—	1.5	—	18.1	14.5
Primary biliary cholangitis/overlap syndromes (%)	—	—	30.1	62	48.6	4.2	45
Sarcoidosis (%)	—	36	11.1	7.5	8.4	1.4	17
Drugs (%)	3	1.3	7.9	3	—	1.4	—
Other causes (%)	—	13.5	—	12.6	—	6.8	11.5
Idiopathic (%)	0	20	11.1	6	36	12.5	—

Causative categories of granulomas as described in recent Western series

First Author	Country	Year	Number of Cases	Granuloma, Number (%)	Immune	Infectious	Drug	Foreign Body	Neoplastic	Idiopathic
Gaya[10,a]	Scotland	2003	1662	63(3.8)	31 (PBC 15, sarcoid 7, AIH 3)	9	6	0	5	12
Sartin[53,b]	United States	1991	Not provided	88 (NA)	24 (sarcoid 19, PBC 4)	9	5	0	3	47
McCluggage[11,c]	Ireland	1994	4075	163 (4)	129 (PBC 90, sarcoid 30)	6	2	1	3	22
Drebber[12,d]	Germany	2008	12,161	442 (3.6)	253 (PBC 215, sarcoid 37)	9	11	0	3	146
Dourakis[13]	Greece	2007	1768	66 (3.7)	51 (PBC 41, sarcoid 5)	8	2	0	1	4
Martin-Blondel[14]	France	2010	471	21 (4.5)	13 (PBC 5, sarcoid 2)	3	0	0	2	3

Certain cases in individual series are reclassified here for the purpose of tabulation.

Abbreviations: AIH, autoimmune hepatitis; NA, not available; PBC, primary biliary cirrhosis.

[a] Two cases of biliary obstruction cited in this report are shown here under idiopathic. Treatment with BCG vaccine was included under drug related.

[b] HCV cases are included under infectious.

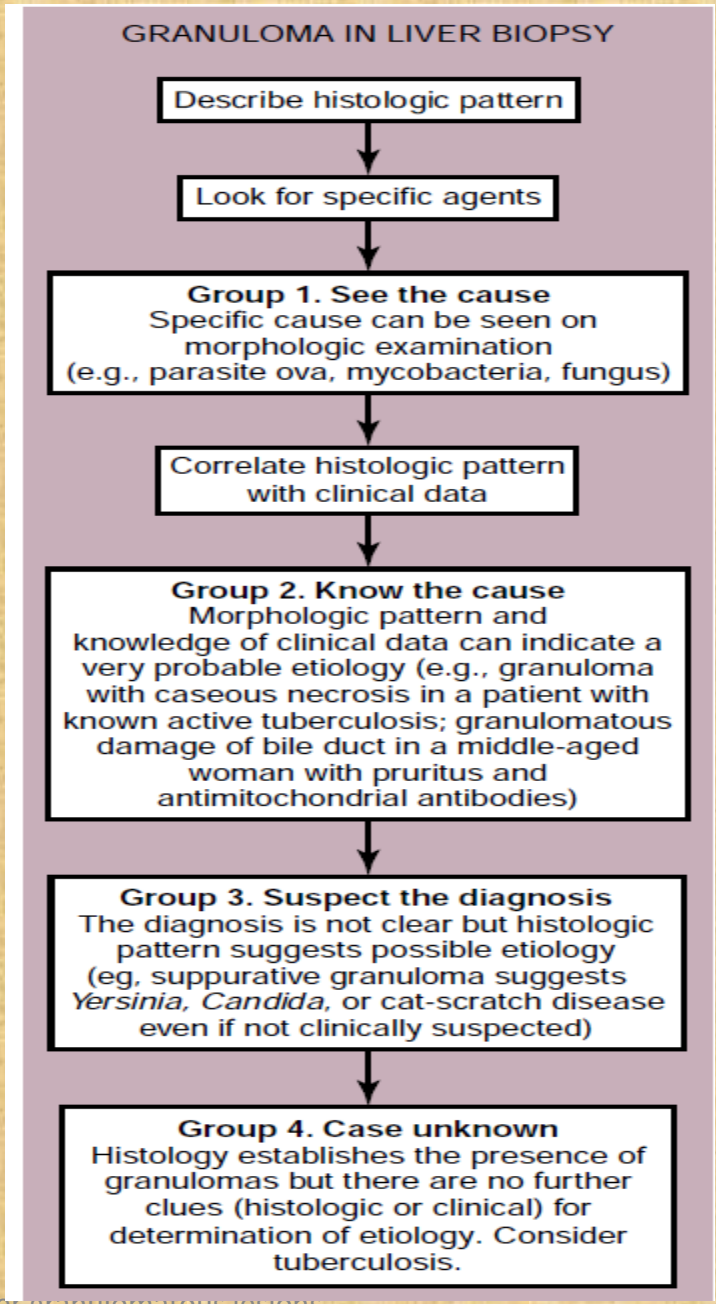
[c] Gout, cryptogenic cirrhosis, and biliary obstruction are included under idiopathic.

[d] Cases of HCV, hepatitis B virus, syphilis, and *Bartonella henselae* are included under infectious. Ulcerative colitis is included under immune.

Granuloma etiologies and characteristics.

Granuloma etiologies	Granuloma characteristics
Autoimmune	
Sarcoid	Noncaseating epithelioid granulomas
Primary biliary cirrhosis	Noncaseating granulomas near portal triads
Infectious	
Mycobacterium tuberculosis	AFB inside epithelioid granulomas and giant cells often with ring of lymphocytes and histiocytes
M avium intracellulare	Aggregates of foamy macrophages in parenchyma and portal triads with +AFB stain
M leprae	Foamy histiocytes in portal tracts and lobules with multiple AFB found
Brucella	Noncaseating granulomas
Rickettsia	Fibrin ring surrounding vesicle of fat
Francisella	Suppurative microabscesses with surrounding macrophages
Listeria	Microabscesses with small granulomas
Bartonella henselae	Stellate abscesses with three distinct zones
Tropheryma whipplei	Epithelioid granulomas
Histoplasma	Macrophages and lymphocytes with histoplasma and epithelioid cells in center
Schistosoma	Eosinophils with fibrosis and collagen deposition in peri-portal and peri-sinusoidal areas often with egg at the center
Leishmania	Fibrin ring or epithelioid granulomas
Hepatitis C	Epithelioid granulomas
Drugs and Chemicals	Granulomas with eosinophils
Malignancy	Non-necrotic granulomas

AFB = Acid-fast bacilli.



Algorithmic approach for the diagnosis and interpretation of hepatic granulomas.

Drugs associated with hepatic granulomas

Miscellaneous	Neurologic	Antimicrobial	Cardiovascular	Biologic	Hypoglycemic	Herbal/ Alternative	Antiinflammatory	Antineoplastic
Allopurinol	Carbamazepine	Cephalexin	Chinidine (antiarrythmic)	Etanercept[52]	Glyburide	Seatone	Aspirin	Procarbazine
BCG	Chlorpromazine	Dapsone	Diltiazem[54]	Peginterferon[40]	Tolbutamide	Green juice[55]	Dimethicone	
Feprazone	Methyldopa	Isoniazid	Disopyramide		Rosiglitazone[56]		Gold	
Contraceptives	Diazepam	Nitrofurantoin	Hydralazine				Phenazone	
Halothane	Phenytoin	Oxacillin	Metolazone				Sulfasalazine	
Mineral oil		Penicillin	Phenprocoumon				Mesalamine[57]	
Papaverine		Sulfa antibiotics	Prajmalium					
Ranitidine			Procainamide					
Quinine			Quinidine					
Propylthiouracil[58]			Tocainide					
Saridon (Excedrin)[59]			Trichlormethiazide					
			Hydrochlorothiazide[60] Clofibrate[61]					

Data from Ishak KG, Zimmerman HJ. Drug-induced and toxic granulomatous hepatitis. Baillieres Clin Gastroenterol 1986;2:463–80.

Rare causes

- Systemic inflammatory and rheumatologic conditions like Wegener granulomatosis and connective tissue diseases such as polymyalgia rheumatica, temporal arteritis, systemic lupus erythematosus, Sjogren disease, and erythema nodosum have been associated with hepatic granulomas.