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The Prevalence and Etiology of Hepatic Granulomas in Turkey: A Systematic Review

Türkiye'de Hepatik Granülomlarin Prevalansı ve Etiyolojisi: Bir Sistematik Derleme

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ABSTRACT Objective: Hepatic granulomas (HGs) are seen in 2-4% of liver biopsies and the etiology is heterogeneous including liver involvement in systemic immunologic disorders and infectious diseases, primary hepatic diseases, drug hepatotoxicity, foreign bodies, and reaction to neoplastic disease. Common etiologies are primary biliary cholangitis (PBC) and sarcoidosis in the Western world, while infections especially tuberculosis (TB) preclude in the Eastern countries. In Turkey, HGs have been reported in 2-5% of liver biopsies and the etiology includes both infections and non-infectious diseases. In this review, we aimed to determine the prevalence and etiology of HGs in Turkey. **Material and Methods:** A search of Pubmed, Scopus and Science Citation Index and national databses (including Tübitak Ulakbim, Türkmedline, and Türk Atıf Dizini) was done and 60 reports were reached. Four studies from Turkey dedicated to describe the rate of HGs and their etiology were determined. **Results:** The rate of HGs is 2.27% (208/9164). Infections as a group (TB, hydatid disease, HCV, brucellosis, fascioliasis, typhoid fever, fungal infection, HBV, actinomycosis, yersiniosis, leishmaniasis, and infectious mononucleosis) were the etiology in 38.4%. PBC was the leading etiology, followed by sarcoidosis, TB, and hydatid disease. Beside the dedicated HG series, 11 series from Turkey included cases with HGs and 45 papers described 52 case reports with HGs. **Conclusion:** HGs are seen in 2.3% of the liver biopsies in Turkey. The infections still represent the leading etiology and among them, TB appears the commonest one. When the cases are evaluated individually, PBC is the leading etiology. Infections are followed by PBC and sarcoidosis, which are main two etiologies of HGs in the world. The local and regional epidemiology of certain infectious diseases, particularly TB determines the etiologic distribution of HGs.

Keywords: Hepatic granuloma; Turkey; primary biliary cholangitis; sarcoidosis

ÖZET Amaç: Karaciğer biyopsilerinin %2-4'ünde, karaciğer granülom (KG)ları görülür. KG'lerin, sistemik immünolojik bozukluklar, enfeksiyon hastalıkları, primer hepatik hastalıklar, ilaç hepatotoksisitesi, yabancı cisimler ve neoplastik hastalığa reaksiyon gibi geniş bir etiyolojisi vardır. Yaygın etiyolojiler, Batı dünyasında primer biliyer kolanjit (PBK) ve sarkoidoz olup, Doğu ülkelerinde ise enfeksiyon hastalıkları, özellikle tüberküloz ön plana çıkmaktadır. Türkiye'de de karaciğer biyopsilerinin %2-5'inde KG bildirilmiş olup; etiyolojisi, hem enfeksiyonları hem de enfeksiyon dışı nedenleri içermektedir. Bu derlemede, Türkiye'deki KG prevalansını ve etiyolojisini belirlemeyi amaçladık. **Gereç ve Yöntemler:** PubMed, Scopus, Science Citation Index ve ulusal indekslerin (TÜBİTAK ULAKBİM, Türk Medline ve Türk Atıf Dizini) araştırması yapıldı ve 60 rapora ulaşıldı. Türkiye'den, KG'lerin oranını ve etiyolojisini tanımlamaya yönelik 4 çalışma belirlenmiştir. **Bulgular:** KG oranı %2,27'dir (208/9164). Grup olarak enfeksiyonlar (tüberküloz, hidatik kist, hepatit C virüsü, bruselloz, fasiolazis, tifo, mantar enfeksiyonu, hepatit B virüsü, aktinomikoz, yersiniyoz, leyişmanyoz ve enfeksiyöz mononükleoz), olguların %38,4'ünün etiyolojisini oluşturmaktadır. Hastalıklar tek tek ele alındığında PBK, önde gelen etiyolojidir ve onu sarkoidoz, tüberküloz ve hidatik kist izlemektedir. KG'ye özgü serilerin yanı sıra Türkiye'den 11 seride, KG içeren olgular vardı. Ayrıca 45 çalışmada, KG'li 52 olgu bildirimi mevcuttu. **Sonuç:** KG'ler, Türkiye'deki karaciğer biyopsilerinin %2,3'ünde görülür. Enfeksiyonlar, hâlâ önde gelen etiyolojiyi temsil etmekte olup, aralarında tüberküloz en yaygın olanıdır. Hastalıklar, tek tek ele alındığında PBK önde gelen etiyolojidir. Enfeksiyonları, dünyadaki KG'lerin ana 2 etiyolojisi olan PBK ve sarkoidoz takip eder. Bazı enfeksiyöz hastalıkların, özellikle tüberkülozun lokal ve bölgesel epidemiyolojisi, KG'lerin etiyolojik dağılımını belirler.

Anahtar Kelimeler: Karaciğer granülomları; Türkiye; safra sirozu; sarkoidoz

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Hepatic granulomas (HGs) are multiple, focal, sharply defined, nodular infiltrates, consisting of modified macrophages (epitheloid cells), surrounded by a rim of mononuclear cells, mainly lymphocytes. HG is seen in %2-4 of liver biopsies and is usually a diagnostic challenge to physicians.[1] HGs may be manifested clinically by abnormal laboratory studies including elevated of serum alkaline phosphatase and gamma glutamyl transferase enzyme levels, or damage to liver structures (eg, intrahepatic bile ducts in primary biliary cholangitis), or progressive liver disease (eg, sarcoidosis).[2] The etiology is heterogeneous including liver involvement in systemic immunologic disorders and infectious diseases, primary hepatic diseases, drug hepatotoxicity, foreign bodies, and reaction to neoplastic disease.[1]

The etiology differs in various geographical regions especially linked to the differing epidemiology of infections and primary hepatic diseases.[3] Referral bias, medical center's characteristics, experts' personal interests, and patient profile may influence the etiologies reported from a single center. HGs may be seen during the course of a primary liver disease or it may represent liver involvement in a systemic disease. Common etiologies are primary biliary cholangitis and sarcoidosis in the Western world, while infections especially tuberculosis preclude in the Eastern countries.[4-12]

In Turkey, HGs have been reported in %2-5 of patient who undergo a liver biopsy and the etiology includes both infections (tuberculosis, hydatid cyst, brucellosis, typhoid fever, chronic hepatitis B and C) and non-infectious diseases (primary biliary cholangitis [PBC], sarcoidosis.[13] In this review, we aimed to determine the prevalence and etiology of HGs in Turkey by the search of medical literature.

MATERIAL AND METHODS

A search of Pubmed, Scopus, Science Citation Index and national databases including Tübitak Ulakbim, Türkmedline, and Türk Atıf Dizini from January 1, 1957 to March 1, 2020 was done with the search terms "liver [MeSH]", "granuloma [MeSH]", "Turkey [MeSH]", "hepatitis [MeSH]", "hepatic", "hepatic granuloma", "granulomatous hepatitis", "Turkiye", "karaciğer granülomu", and "hepatik granüloma".

The studies, case series, case reports, and letter to editors were included. Repeat reports, congress abstracts, and reviews were excluded.

The study was approved the Board of Ethics of Medilife Hospital (10.12.2019/No:EK-01).

RESULTS

Literature search revealed 60 reports (Figure 1).

Four studies from Turkey dedicated to describe the rate of hepatic granulomas and their etiology were determined (Table 1).[14-17] These studies found the rate of HG in a range of 1.31% to 6.05%. In 3 series including the largest one, primary biliary cholangitis (PBC) was the leading etiology. When all 4 series considered together, the rate of HGs is 2.27% (208/9164). PBC was the leading etiology, followed by sarcoidosis, tuberculosis, and hydatid disease. These 4 etiologies corresponded to %70 (133 out of 190) of the cases.

Infections (TB, hydatid disease, HCV, brucellosis, fascioliasis, typhoid fever, BCGitis, fungal infection, HBV, actinomycosis, yersiniosis, leishmaniasis, and infectious mononucleosis) were the etiology in 38.4% (73 out of 190) of the cases.

Beside the dedicated HG series, 11 series from Turkey included cases with HGs (Table 2).[18-28] Among them, one was a review of radiological features of 8 cases with HG [18]. One series of fever of unknown origin described one patient with HG and another series of living-related liver donor described two patients with HGs.[23,25] The others were series of miliary TB, TB granulomas, HBV, HCV, brucellosis, and abdominal sarcoidosis.

Forty-five papers from Turkey have described 52 patients with HGs (Table 3).[29-74]

DISCUSSION

HGs are seen in 2.27% of liver biopsies in the country. The prevalence may change according to the characteristics of medical unit and the physician. HGs are seen in a high rate in some diseases including PBC, sarcoidosis and tuberculosis and the centers

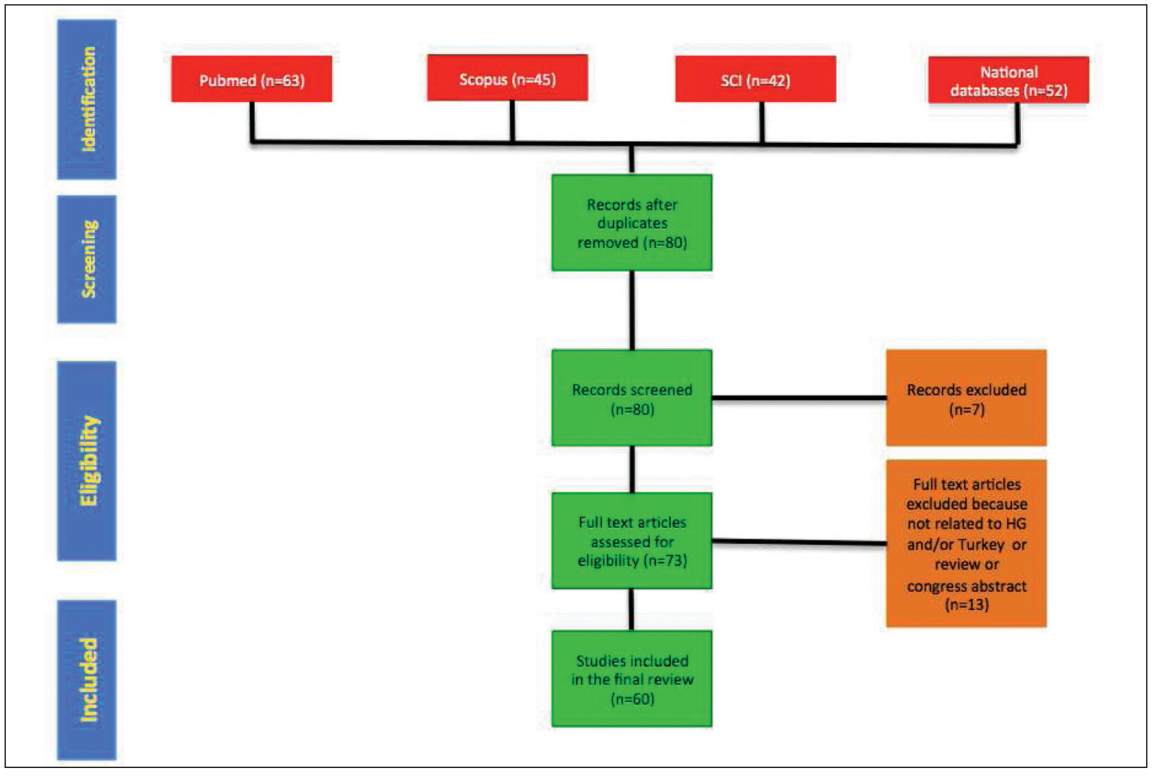

FIGURE 1: Flow diagram for literature search.

caring the patients with such diseases detect and report relatively higher rates of HG.

Liver biopsy is an invasive method used for diagnosis, grading and staging of liver diseases.[75] It is less commonly performed after the clinical use of imaging and laboratory studies. It is limited to the diseases where multiple etiologies are suspected, abnormal liver tests of unknown etiology, cryptogenic liver disease, severe portal hypertension with no liver dysfunction, and focal liver abnormalities on imaging.[76] Generally such cases are referred to tertiary care centers and HGs are commonly reported from university hospitals or education and training hospitals in the country.

In the diagnosis, grading and staging of chronic hepatitis B and C, liver biopsy is commonly replaced by non-invasive tests. However these tests may not be available in some centers and not reimbursed. Also chronic hepatitis treatment is reimbursed only with a histological proof of the disease. These practices increase the relative role of HBV and HCV in the etiology of HGs.[16,17,22,24]

PBC is a chronic progressive cholestatic granulomatous, and destructive inflammatory lesion of the liver. HGs are common histological findings in PBC and they are suggested to result from the interaction between immature dendritic cells and IgM.[77] PBC is the leading etiology of HGs in series from Turkey accounting 30% of the cases. PBC diagnosis is established by anti-mitochondrial antibody (AMA) positivity. However in approximately % 5to %10 of the patient, AMA is absent or present only low titer and liver biopsy is diagnostic in this group.[78]

Sarcoidosis is the second most frequent etiology of HGs. It is a multisystem disease characterized by non-caseating granulomas in affected organs, mainly in the lungs. Beside pulmonary system, the reported prevelance of hepatic involvement by sarcoidosis varies considerably across studies, ranging from %5 to %30. Since liver involvement in most of the patients is asymptomatic, the majority of cases are diagnosed incidentally, frequently by the finding of elevated liver enzymes. Liver biopsy is usually used to confirm the diagnosis especially when the pulmonary involve-

TABLE 1: Dedicated studies from Turkey describing the rate of hepatic granulomas and their etiology.

No	Authors (Reference)	Year	Rate	Male/ Female	Mean Age (years)	Etiology PBC	Sarcoidosis	TB	HD	Others
1	Mert et al.[14*]	2001	74/4490 (1.6%)	26/30	30		20	11	5	unknown 11, brucellosis 3, typhoid fever 2, HCV 1, IM 1, Hodgkin's disease 1, drug 1
2	Onal et al.[15]	2008	13/592 (2.2%)	5/8	40	3	2	2		BCGitis 2, unknown 2, HL 1, fungal infection 1
3	Turhan et al.[16]	2011	86/1420 (6.05%)	23/63	48.6	38	4	10	16	HCV 4, foreign body 3, HCC 2, NHL 1, HL 1, cholangiocellular carcinoma 1, actinomycosis 1, yersiniosis 1, fascioliasis 1, fungal infection 1, drug 1, unknown 1
4	Sahin et al.[17]	2014	35/2662 (1.31%)	8/27	51.6	16	6			fascioliasis 2, HCV 2, HBV 2, AIH 2, TB+RA 1, TB+ brucellosis 1, leishmaniasis 1, HL 1, IC 1
TOTAL			208/9164 (2.27%)	62/128	42.9	57	32	23	21	unknown 14, HCV 7, Hodgkin's disease 4, brucellosis 3, fascioliasis 3, foreign body 3, typhoid fever 2, drug 2, BCGitis 2, fungal infection 2, HCC 2, HBV 2, AIH 2, NHL 1, cholangiocellular carcinoma 1, actinomycosis 1, yersiniosis 1, TB+RA 1, TB+ brucellosis 1, leishmaniasis 1, IC 1, IM 1

*It represents the data of 56 out of 74 patients who had files available.

PBC: Primary biliary cholangitis, HD: Hydatid disease, TB: tuberculosis, HCV: Hepatitis C virus, IM: Infectious mononucleosis, BCG: Bacillus Calmette-Guérin, HL: Hodgkin's lymphoma, HCC: Hepatocellular carcinoma, NHL: non-Hodgkin's lymphoma, AIH: Autoimmune hepatitis, RA: Rheumatoid arthritis, IC: Immune cholangiopathy.

TABLE 2: Reported series from Turkey containing hepatic granulomas.

No	Authors (Reference)	Year	Remarks
1	Balci et al.[18]	2001	A review of radiological features of 8 patients (4 sarcoidosis, 2 TB, 2 unknown) with granulomatous hepatitis
2	Kaplan et al.[19]	2001	A review of 43 patients with eosinophilic hepatic granuloma included 1 patient from Turkey
3	Mert et al.[20*]	2001	In a miliary tuberculosis series of 38 patients, liver biopsy was available in 15 and all had HG.
4	Mert et al.[21*]	2003	In a series of tuberculous granulomas, Ziehl-Neelsen staining and polymerase chain reaction study were performed in 8 liver samples
5	Ozaras et al.[22]	2004	Among liver biopsy samples of 605 cases with chronic hepatitis C, hepatic granulomas were found in 8 cases (1.3%).
6	Saltoglu et al.[23]	2004	Among 87 patients with fever of unknown origin, 1 patient had granulomatous hepatitis (the etiology was not reported)
7	Tahan et al.[24]	2004	Among liver biopsy samples of 663 cases with chronic hepatitis B, HGs were found in 10 cases (1.5%).
8	Savas et al.[25]	2008	Among 201 living-related liver donors, liver biopsy showed 2 cases with granulomatous reactions.
9	Gezer et al.[26]	2015	In a review of abdominal sarcoidosis, 4 cases of biopsy-proven hepatic sarcoidosis were reported
10	Suvak et al.[27]	2016	Among patients with brucellosis, 15 out of 95 showed HGs
11	Mert et al.[28*]	2017	In a miliary tuberculosis series of 263 patients, liver biopsy was available in 21 and all had HG.

TB: Tuberculosis, HG: Hepatic granuloma. *These reports may contain overlapping cases.

TABLE 3: Case reports of hepatic granulomas reported from Turkey.

No	Authors (Reference)	Year	Age (years)	Gender	Etiology
1	Gundogdu et al.[29]	1992	7	Female	TB
2	Emre et al.[30]	1992	24	Male	TB
3	Ozbakkaloglu et al.[31]	1999	46	Male	BCG (intravesical)
4	Mert et al.[32]	2001	46	Female	HCV infection
5	Erten et al.[33]	2003	27	Female	Sarcoidosis
6	Mert et al.[34]	2003	19	Female	TB
7	Akcay et al.[35]	2004	23	Female	TB
8	Mert et al.[36]	2004	53	Female	Typhoid fever
9			66	Male	Typhoid fever
10	Sen et al.[37]	2004	70	Male	TB
11	Soylu et al.[38]	2004	17	Male	Sarcoidosis
12	Akcam et al.[39]	2005	12	Female	TB
13	Poyanli et al.[40]	2005	41	Female	Foreign body
14	Akay et al. [41]	2006	50	Female	Sarcoidosis (during interferon treatment of HCV infection)
15	Dede et al.[42]	2006	29	Male	TB
16	Ersoy et al. [43]	2006	42	Male	BCG (intravesical)
17			56	Male	BCG (intravesical)
18	Inan et al. [44]	2006	5	Male	Toxocariasis
19	Koksal et al.[45]	2006	48	Male	TB
20	Parsak et al. [46]	2008	30	Female	TB
21			63	Male	TB
22	Yazici et al. [47]	2008	43	Female	Visceral leishmaniasis
23	Alabaz et al. [48]	2009	8	Male	Fungal infection (Exophiala dermatitidis)
24	Egritas et al. [49]	2009	10	Male	HCV infection
25	Dursun et al. [50]	2009	15	Female	TB
26	Soylu et al. [51]	2009	46	Male	BCG (intravesical)
27	Cetinkaya et al. [52]	2010	40	Male	Actinomycosis
28	İnce et al [53]	2010	26	Female	Fasciolasis
29			50	Female	Fasciolasis
30	Önal et al.[54]	2010	58	Male	BCG (intravesical)
31	Ozin et al.[55]	2010	43	Female	TB
32	Sevinc et al.[56]	2010	23	Female	Inflammatory myofibroblastic tumor
33			29	Male	Inflammatory myofibroblastic tumor
34	Karaman et al. [57]	2011	5-month-old	Male	Xanthogranulomatous pyelonephritis and liver lesion
35	Şişman et al.[58]	2011	55	Female	PBC
36	Haltaş et al.[59]	2012	35	Male	Brucellosis
37	Anar et al.[60]	2013	27	Female	TB
38	Ekiz et al.[61]	2014	41	Male	Unknown
39	Tasbakan et al.[62]	2014	51	Female	Sarcoidosis
40	TurkelKucukmetin et al.[63]	2014	42	Female	TB*
41	Caliskan et al.[64]	2015	4	Male	TB
42	Kayar et al.[65]	2015	30	Female	TB
43	Ufuk et al.[66]	2015	67	Female	Sarcoidosis
44	Koklu et al.[67]	2016	71	Female	Sarcoidosis
45	Eren Akarcan et al.[68]	2017	16	Male	CGD
46	Koklu et al.[69]	2018	68	Male	Sarcoidosis
47	Özgüven et al.[70]	2018	53	Female	Sarcoidosis
48	Yildirim et al.[71]	2018	54	Male	Brucellosis
49	Bayramoğlu et al.[72]	2019	15	Female	CGD
50	Samdanci et al.[73]	2019	26	Female	Fasciolasis
51			52	Female	Fasciolasis
52	Kocabas et al.[74]	2020	8	Male	Tularemia
TOTAL: 52 cases		1992-2020	Age: 36 ± 19 years	Male 25/ Female 27	TB 16, sarcoidosis 8, BCG (intravesical) 5, fasciolasis 4, HCV infection 2, typhoid fever 2, brucellosis 2, CGD 2, inflammatory myofibroblastic tumor 2, foreign body 1, toxocariasis 1, visceral leishmaniasis 1, fungal infection 1, actinomycosis 1, xanthogranulomatous pyelonephritis and liver lesion 1, unknown 1, tularemia 1

BCG: Bacillus Calmette-Guérin, HCV: hepatitis C infection, TB: tuberculosis, CGD: chronic granulomatous disease. *Described a patient from Georgia.

ment is not characteristic and diagnostic. Sarcoidosis is seen in Turkey, with an incidence of 4/100 000.[79] The diagnosis of extrapulmonary involvement of sarcoidosis mostly depends on the histology and non-caseating granulomas are detected in the tissues.

Infectious diseases are the cause of HGs in %37 (71/190) in series and %70 (30/43) in case reports in the country. Among infections, especially TB constitutes the largest part. TB is endemic in the country with an incidence of 17/100 000.[80] While pulmonary cases are diagnosed with bacteriological studies and imaging, the diagnosis of hepatic TB is challenging and is generally based on histologic and bacteriologic studies of the liver biopsy. Caseating granulomas are the characteristic histologic findings. Among the etiology of HGs, TB is the leading one in the countries where TB is prevalent.[10-12]

The etiology of HGs shown significant differences among countries: The most frequent etiology is PBC in the United Kingdom, Greece, Germany, and Northern Ireland, while it is TB in Iran, India, and Portugal.[4-7,9,11,81] The etiology may change with time as the infectious diseases are controlled. In France, the leading etiology of HGs (24/73 of the cases) was reported TB in 1984, while PBC was the commonest one with only one TB out 21 cases in 2010.[82,83] In Saudi Arabia, schistosomiasis was reported in more than half of the HGs in 1990, while another report for years 1993-2005, it was reported in 5%.[8,12] Despite detailed search, the etiology of HGs remains unknown in some patients. It is %7.4 [14/190] in series reported from Turkey. The relatively higher rate of unknown etiology in earlier series (11/74, %14.9 in 2001 and 2/13, %15.4 in 2008) [14,15] seemed to decrease in more recent series (1/86, %1.2 in 2011, and 0/35 in 2014).[16,17]

CONCLUSION

HGs are seen in %2.3 of the liver biopsies in Turkey. The infections still represent the leading (%38) etiology and among them, TB appears the commonest one. Infections are followed by PBC and sarcoidosis, which are main two etiologies of HGs in the world. The local and regional epidemiology of certain infectious diseases, particularly TB affects the etiologic distribution of HGs.

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Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

All authors contributed equally while this study preparing.

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