

## Letter to the Editor

## Causes of Hepatic Granuloma: A 12 Year Single Center Experience from Southern Iran

Dear Editor,

We have read with interest the recently published article by Geramizadeh et al.<sup>1</sup> in your journal. There are a few published data regarding the etiology of granuloma in Iran. Hepatic granuloma could be idiopathic or caused by a unique inflammatory response to a variety of antigens including bacteria, fungi, parasites, viruses, and drugs or even self-antigens. It could also be a presentation of underlying malignancy.<sup>2,3</sup>

The study by Geramizadeh et al. was a retrospective study, which has some limitation for inclusion of all causes of liver granuloma. The authors did not present the number of liver blocks for review, and the percentage of the positive cases is not known. Considering the fact that thousands of liver biopsies are conducted in Shiraz, referral hospitals finding 72 cases of granuloma shows the prevalence is not as high as claimed.

Furthermore, the authors found that 12.5% of enrolled cases were idiopathic hepatic granulomas. We would like to add that other infections such as brucellosis, which may present with a fever of unknown origin (FUO), can be a cause of liver granuloma.<sup>4</sup> Brucellosis with *brucella abortus* type is the most common species that can cause hepatic granulomas which are indistinguishable from sarcoidosis.<sup>3</sup> We are not certain that PCR in paraffin embedded liver tissue can exclude brucellosis as the cause of liver granuloma in the study group. Moreover, hepatitis C infection is an emerging disease in Iran, but the testing became routine in Iran in 1996. Anti-HCV Ab, as a screening test, cannot exclude HCV-infected cases and molecular studies for PCR in the serum or PBMC are necessary.<sup>5</sup> The granuloma in HCV-infected cases is more common in intravenous drug users and those co-infected with HIV and perhaps it is related to the impurity of the drugs used. The authors did not present any data regarding risk factors and the socioeconomic aspects of the patients.

Many drugs can cause hepatic granuloma, and diagnosis of these cases in a retrospective study is not easy. At least some of the idiopathic cases in this report could be drug induced.<sup>6</sup> There are also reports of hepatic granuloma formation even with toxic material exposure, such as phosphine, from Iran.<sup>7</sup> In this study we were not informed about the type of the granuloma. In some reports necrotizing granuloma was more likely to be associated with infectious etiologies, while perigranuloma fibrosis was more common in sarcoidosis.<sup>8</sup> This may help to target the work up in centers where molecular or immunohistochemical studies are not readily available.

In conclusion, although this study highlighted the importance of tuberculosis as a major cause of hepatic granuloma, at least in southern part of Iran, it has limitations in excluding other etiologies such as brucellosis and HCV with or without HIV coinfection.

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### Author's Reply

First of all, I should emphasize that although there are a few case reports about hepatic granuloma from Iran, there is no report that contains as many cases of pathology proven granuloma in the liver during 12 years.

1) Dr. Lankarani has criticized our paper because of the assumption that we have not presented the number of positive cases, but we have mentioned that in 3142 liver biopsies over 12 years there were 72 cases (2% – 3%) of hepatic granuloma.<sup>1</sup> This percentage is very close to other reports (2% – 15%) from throughout the world (Table 1).<sup>2</sup>

2) Brucellosis was the second concern by Dr. Lankarani. I would like to emphasize the rarity of hepatic involvement in brucellosis. Although brucellosis is a common disease in Iran, even in endemic countries liver involvement is considered an unusual manifestation of brucellosis.<sup>1,2</sup>

3) In consideration of HCV as a cause of hepatic granuloma in our cases, I would like to refer again to Table 1. The worldwide percentage is 1.8% to 14.8%. In our cases this percentage was 4.2%. Meanwhile, in 7 out of 9 cases with no known cause for hepatic granuloma, we checked for HCV. The results were negative; therefore we do not believe this would be lower than expected.

4) Regarding drugs as a cause of hepatic granuloma; according to our experience it is not a common cause, and more importantly this should be after the exclusion of all other causes. We agree with Dr. Lankarani that there is always the possibility<sup>3,11</sup> of a new drug that

**Table 1.** The most common causes of hepatic granuloma in different locations worldwide.

Country	Iran	Iran, children <sup>3</sup>	Saudi Arabia <sup>4</sup>	UK <sup>3</sup>	Scotland <sup>5</sup>	Greece <sup>6</sup>	Ireland <sup>7</sup>	USA <sup>8</sup>	Australia <sup>9</sup>	Turkey <sup>10</sup>	Germany <sup>11</sup>
Study period	2008–1996	2005–1996	2008–1993	2001–1991	1979–1970	2004–1999	1992–1980	–1976 1985	1968–1984	2006–2003	2004–1996
Granulomas (n)	72	33	807	63	77	66	63	88	59	13	424
Hepatic granulomas (%)	2.3	-	14.6	-	-	3.7	4	-	-	2.2	3.63
Mean age (years)	24	3.1	46.4	42	-	57	-	54.2	-	44	-
Male (%)	54.2	45.5	64	33.4	-	23	-	49	-	38	-
Female (%)	45.8	54.5	36	74.6	-	77	-	51	-	62	-
Mycobacterial (%)	51.4	45.5	42.6	4.8	10.4	1.5	1.8	3	7	15	0.007
VL <sup>1</sup> (%)	8.3	3	-	-	-	1.5	-	-	-	-	-
VLM <sup>2</sup> (%)	4.2	-	-	-	-	-	-	-	-	-	-
Fungal infection (%)	4.2	-	-	-	-	-	-	-	-	7.5	-
Hepatitis C (%)	4.2	3	14.8	9.5	-	4.5	-	-	-	1.8	-
PBC <sup>3</sup> (%)	4.2	-	-	23.8	-	62	55	4.5	-	23	48.64
AIH <sup>4</sup> (%)	2.8	-	-	4.8	-	6	-	-	-	-	-
Drug-induced (%)	1.4	-	1.6	9.5	-	3	1.2	6	7	-	2.48
Foreign body (%)	1.4	-	-	-	-	-	-	-	-	-	-
BCGitis (%)	1.4	-	-	-	-	-	-	-	-	15	-
CMV <sup>5</sup> (%)	1.4	-	-	-	-	-	-	-	-	-	0.005
Sarcoidosis (%)	1.4	6.1	5	11.1	10.4	7.5	18	22	12	15	8.37
Neoplasm (%)	1.4	-	3.2	6.3	7.8	1.5	1.2	3.4	8	7.5	-
Brucellosis (%)	-	-	1.6	-	-	-	-	-	-	-	-
Crohn's disease (%)	-	-	3.3	-	-	-	1.8	-	-	-	-
Vasculitis (%)	-	-	-	-	-	1.5	-	-	-	-	-
Hepatitis B (%)	-	-	3.3	-	-	3	-	-	1.6	1.9	-
Idiopathic (%)	12.5	42.4	14.8	11.1	31	6	11	50	29	15	64

<sup>1</sup>VL = Visceral leishmaniasis; <sup>2</sup>VLM = Visceral larva migrans; <sup>3</sup>PBC = Primary biliary cirrhosis; <sup>4</sup>AIH = Autoimmune hepatitis; <sup>5</sup>CMV = cytomegalovirus

could cause an unusual manifestation in the liver.

Finally, I would like to direct your attention to Table 1 again, which is a comparison between our results with other areas of the world.

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## Alarming Rise in Cesarean Section in Iran

Dear Editor,

I read with interest the papers by Badakhsh et al,<sup>1</sup> Ostovar et

al.<sup>2</sup> and the editorial by Sepanlou and Akbarian<sup>3</sup> in the January 2012 issue of Archives of Iranian Medicine. The first paper confirmed our previous finding of the unexpected significantly high rate of cesarean section in Tehran.<sup>4</sup> In a longitudinal community-based study<sup>5</sup> the Tehran Lipid and Glucose Study (TLGS), during 3 years of follow up we reported that in 411 live birth deliveries, there were 86% cesarean sections, while only 14% had normal deliveries. The population of TLGS is representative of Tehran's population according to data from the Iran Statistical Center<sup>5</sup> and have been followed for evaluation of trend of prevalence of risk factors of non-communicable disease, as well as registration of any event ending to hospitalization or death. Every single event occurring in any family of TLGS is recorded yearly, followed by meticulous evaluation of hospital records and other medical data and confirmed by members of the "outcome" committee.<sup>6</sup>

With the high rate of cesarean section in a public hospital in Tehran<sup>1</sup> and in TLGS<sup>4</sup>, even if 47.2% of all cesarean sections were to be considered appropriate,<sup>2</sup> the rate of inappropriate cesarean section would still be very high in Iran.

Both groups of authors<sup>1,2</sup> have warned against rising rates of cesarean section in Iran and have advised for addition of immediate strategies to prevent the rising trend of unnecessary cesarean sections in Iran. Although the rate of request for a cesarean section by women was high in the study by Ostovar et al., this comprised only 15.6% of all cases;<sup>2</sup> therefore, the majority of decisions made to perform cesarean are influenced by the obstetricians. In addition to huge difference of payments for cesarean section and normal vaginal deliveries, normal daytime schedule for cesarean section as opposed to the unexpected, usually nighttime, performance of normal vaginal deliveries may contribute to the trend in decision towards cesarean section, which in our study, had been made and the pregnant women were notified more than 4 months prior to delivery in 73% of cases.

The WHO has considered medical or scientific justification for cesarean section in 15% of deliveries.<sup>7</sup> The rate of cesarean section has increased from 25% in 1988 to 30.2% in 2005 in USA<sup>8</sup> and from 13.8% in 1994 to 18.1% in 1999 in Sweden;<sup>9</sup> however, the rates are still much lower than what is observed in Iran.

The editorial note has wisely summarized the finding of both articles and has agreed with high rates of cesarean section and wide range of strategies that should be adopted to limit the growing rate of cesarean sections in Iran. In addition, they concluded that since overall maternal mortality rate has actually decreased, during the past three decades in Iran, one should hesitate for a moment before reacting to these reports.<sup>3</sup> I tend to disagree with this editorial conclusion. In the Islamic Republic of Iran, in the last 3 decades, all health indicators have shown significant improvement. The rate of infant mortality has decreased from 51 to 29 and under 5 mortality rate decreased from 60 to 22 per 1000.<sup>10</sup> Iodine deficiency disorders have been eliminated<sup>11</sup> and the rates of many communicable and non-communicable diseases have decreased. This improvement in health care indices are mostly due to more comprehensive health care network, with access to primary health care, public education and improvement of household economy.<sup>9</sup> Therefore, such a decrease in overall maternal mortality could not be attributed to the rising trend of cesarean section. It may be argued that the rising trend of cesarean section may have been a questionable factor, hindering a more appropriate fall in this very important health indicator.

As physicians, we must avoid any unnecessary medical perfor-

mance that may harm the patient and should always act unhesitatingly if the benefits outweigh the hazards, and the cesarean section is definitely no exception!

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## Author's Reply

In reply to Dr. Azizi letter, a number of points are worth mentioning. There is no disagreement on the fact that the decrease in maternal mortality rates has been in the most part achieved as a result of comprehensive health network, access to primary health care, and improvements in socio-economic status.<sup>1</sup> Neither is there any disagreement on the rising risk of inappropriate cesarean sections when rates increase to above 15%,<sup>2</sup> nor on the necessity of relevant health policies in this regard. These points are all mentioned in the editorial as well. The mainstay of the last sentence of the editorial, which has not been fully explained there, can be summarized into the following:

1) Previous studies on rates of cesarean section have been done in the city of Tehran, where most hospitals and especially public ones are referral centers.<sup>3,4</sup> As mentioned in the editorial, the demographic patterns highly influence the acceptable rates of cesarean section.<sup>5</sup> The fact should be noticed that complicated deliveries are usually referred to public hospitals in Tehran and cesarean section may be indicated for most of them. Therefore, rates higher than usual are logically acceptable in these centers.

2) The second much more important point is related to the fact that in addition to primary care, secondary care of mothers has contributed to improved health indicators as well.<sup>1</sup> Studies are mandatory to determine the rates of Cesarean Section in deprived

regions of the country and the percentage of complicated deliveries with absolute indication for Cesarean Section that would have been done by midwives instead of obstetricians and by vaginal delivery. More detailed studies are needed to determine the outcome of these deliveries and their trend during the past 30 years.

In short, judgments made exclusively on rates of Cesarean Section in public hospitals in Tehran can be quite misleading. It is documented that in regions with higher socio-economic status where women are more educated, more probably employed, and affluent enough to afford the costs of Cesarean Section,<sup>6</sup> the rates of elective and unnecessary sections rise.<sup>5</sup> We should be able to differentiate elective sections from those which are absolutely indicated and to plan policies accordingly in order not to harm either side: the poor and the rich.

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