

# Ferritin levels in cirrhotic and malignant ascites

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*The diagnostic usefulness of ferritin measurements in cirrhotic and malignant ascites has been evaluated in 61 patients. In 22 patients with malignant disease, median ferritin concentration was 833 ng/ml in the ascitic fluid. In 39 patients with ascites from liver cirrhosis corresponding value was 108 ng/ml. There was statistically significant difference between these values ( $p<0.01$ ). Discriminative value of ferritin levels ( $>375$  ng/ml) in malignant and cirrhotic ascites were calculated. Diagnostic specificity and diagnostic sensitivity were 81.8%, 89.7% respectively. These results indicate that the measurement of ferritin levels may be useful aid in differential diagnosis of cirrhotic and malignant ascites. [Turk J Med Res 1994; 12(6): 236-238]*

Key Words: Ascites, Neoplasm, Ferritin

Ferritin, an iron storage protein with a molecular weight of about 450 000 Dalton, is found mainly in the liver and reticuloendothelial system. Trace amounts of ferritin are normally present in the serum and other body fluids. In healthy adults the concentration of ferritin in serum positively correlated with the iron stores in the body (1). Increased serum concentrations of ferritin have been found in patients with iron overload, severe liver disease, especially in alcoholic liver disease and viral or drug induced hepatic necrosis (2). In the inflammatory response, ferritin possibly behaves as an acute phase protein and increased concentration of ferritin has been found in a number of inflammatory diseases (3).

High concentrations of serum ferritin have also been reported in a number of malignant disorders such as lymphoma, acute leukemia, multiple myeloma, breast, testicular, head and neck, hepatocellular, lung, thyroid, colon and pancreatic cancers (4-10).

Ascitic fluid ferritin levels has been proposed and investigated as a marker of malignant ascites previously (11-13). In the current study, we examine the potential usefulness of ferritin measurements in ascitic

fluids in the differential diagnosis of malignant and cirrhotic ascites.

## MATERIALS AND METHODS

The current study includes 61 patients admitted to Hacettepe University, School of Medicine hospital. Thirty nine patients have cirrhotic ascites (28 males and 11 females) with a mean age of  $49.6\pm 17.5$  years (range 21 to 78) and 22 patients have malignant ascites (14 males and 8 females) with a mean age of  $54.3\pm 13.9$  years (range 26 to 74). Diagnostic evaluation was done and cause of ascites was determined for each patient from clinical, laboratory and radiologic findings. Histologic confirmation was present in all of the patients. Patients were divided into two groups according to the nature of ascites. Patients with malignant ascites have the following primary causes; 13 primary peritoneal tumors, 4 colon cancers, 2 pancreatic cancers, 2 ovarian cancers, 1 gastric cancer. Benign ascites were transudate of liver cirrhosis origin.

Ferritin in ascites was measured by ELISA method (IMX system metabolic assays, Abbott, Germany). The normal range of serum ferritin using this method was 20-250 ng/ml. Ascitic fluid cut-off value of ferritin was accepted as 375 ng/ml (one and half of the upper limit of the normal).

Statistical significance was tested by Mann-Whitney U test. Patients with high ferritin concentration in

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malignant ascites (a) and cirrhotic ascites (b) and low ferritin concentration in malignant ascites (c) and cirrhotic ascites (d) were determined. Diagnostic specificity (predictive value of a positive test) was defined as  $a/a+b*100\%$  and diagnostic sensitivity (predictive value of a negative test) as  $d/c+d*100\%$ .

**RESULTS**

Patients with malignant ascites had significantly higher median ferritin concentration than patients with cirrhotic ascites ( $p<0.01$ ). Table 1 gives the median concentrations of ferritin in ascites for each group of patients. Table 2 describes the diagnostic specificity and diagnostic sensitivity of ferritin measurements in malignant and cirrhotic ascitic fluids.

Figure 1 shows the concentrations of ferritin in ascitic fluid of patients with malignant and cirrhotic diseases. High ferritin concentrations ( $>375$  ng/ml) have been found in 18 out of 22 malignant ascites and 4 out of 39 cirrhotic ascites. Malign ascites with normal ferritin concentrations are two primary peritoneal tumors, one colon cancer and one ovarian cancer.

**DISCUSSION**

When ascitic fluid is the presenting symptom, extensive investigations are often initiated to identify the underlying cause. Establishing the malignant nature of serous effusions is often difficult and traditionally based on clinical evidence, the presence of malignant cells and histologic examination. Because of the difficulty in demonstrating malignant cells in effusions, various biochemical markers have been employed in the past to identify malignant effusions (14,15). Although these may provide useful information, they lack specificity. If the diagnosis is not obvious from the clinical presentation, a simple, quick and reliable test of ascitic fluid is essential.

**Table 1.** Median concentrations of ferritin in malignant and cirrhotic ascites

Groups	Patients (n)	Median level (ng/ml)
Malignant ascites	22	833
Cirrhotic ascites	39	108

**Table 2.** Discriminative value of ferritin levels in malignant and cirrhotic ascites

Groups	Ferritin (>375 ng/ml)	Diagnostic Sensitivity (%)	Diagnostic Specificity (%)
Malignant ascites versus Cirrhotic ascites	18/22	89.7	81.8

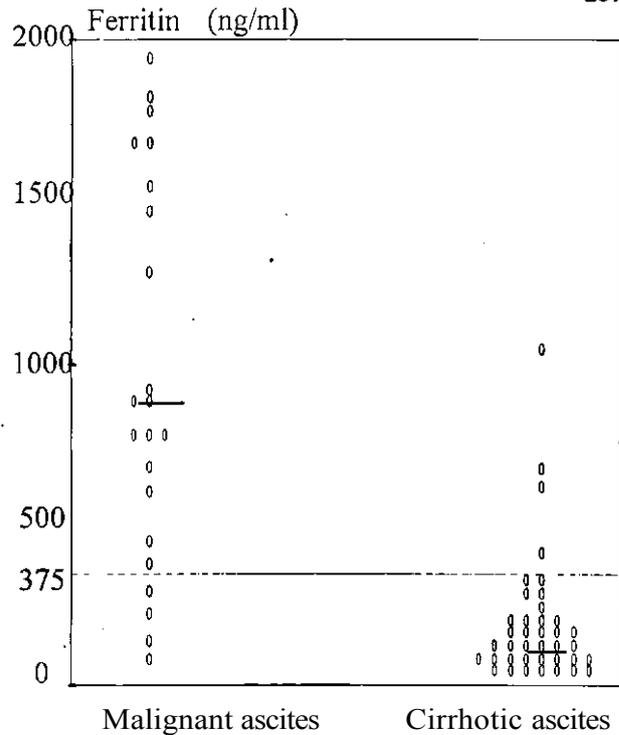


Figure 1. Ferritin concentrations in malignant and cirrhotic ascites

High levels of ferritin is observed in exudative effusions of malignant and non-malignant natures (16,17). But there are some contrary opinions on the use of effusion ferritin level in the discrimination of malignant and nonmalignant exudates. Some authors say that it can be a useful aid in the differential diagnosis of malignant and non-malignant exudates; some say that there were no difference between malignant and non-malignant effusion's ferritin level (12,17). Since our study were done on patients with liver cirrhosis of gastroenterology clinic, it lacks a non-malignant exudative group and it is hard to make a conclusion on this point.

Several mechanisms may be responsible for the increased concentrations of ferritin associated with malignant disease. These include the increased synthesis of ferritin associated with inflammation increased secretion of ferritin by malignant cells (18) and hepatocellular necrosis caused by liver metastases. Increased ferritin concentrations, in turn, may affect the immune system by altering T cell function (19).

The source of ferritin in ascites is unknown. Many of the proteins encountered in effusions are derived from the plasma. The concentration of such proteins in effusions depends primarily on the degree of membrane permeability and molecular size. Although increased serum ferritin levels often associated with malignant disease, it is unlikely that the origin of ferritin in ascites is serum ferritin. Firstly, no correlation has been found in previous studies between concentration of ferritin in ascites and in serum. Secondly,

because of its large size, it is unlikely that the ferritin molecule may pass through peritoneal membrane to any significant extent. Furthermore, local ferritin concentrations exceeding many times those found in the serum can not be assumed to originate from the circulation. By exclusion the main source of ferritin in ascitic fluid seems to be in situ production. Whether the direct source of ascitic ferritin is increased secretion by macrophages, disintegration of malignant or inflammatory cells, or specific production by malignant tissues is at present unknown. No correlation between specific tumor types and the level of ferritin in the ascites could be discerned. In view of the overlap between ferritin concentrations obtained in nonmalignant inflammatory ascites and malignant ascites, the most likely source of ferritin in malignant ascites were inflammatory cells stimulated by the presence of tumor (12).

In conclusion, the measurement of ferritin levels may be a useful tool in the differential diagnosis of malignant ascitic fluids from cirrhotic ascites. But in general, the specificity of test for malignancy is limited. It is possible that the introduction of selective monoclonal antisera for the recognition of various isoferritins may increase the specificity of ferritin measurements in exudates and allow a distinction between tumor-derived ferritin and nonspecific ferritin produced by inflammatory cells.

#### Sirotik ve malign asitlerde ferritin düzeyi

*Malign ve sirotik asiti olan 61 hastada asit ferritin düzeyi ölçümlerinin ayırıcı tanısındaki önemi araştırıldı. Peritoneal karsinomatozise bağlı malign asiti olan 22 hastada ve karaciğer sirozuna bağlı benign asiti olan 39 hastada asitik sıvı ferritin düzeyi ölçüldü. Sirotik asit grubunda 4 hastada (%10), malign grupta 18 (%81) hastada ferritin düzeyleri cut-off değerinin üzerindeydi. Malign asit ferritin düzeyi median değeri 833 ng/ml, sirotik asit median değeri 103 ng/ml olarak bulundu. Malign asit grubundaki bu yükselme istatistik olarak anlamlıydı ( $p < 0.01$ ). Ferritinin malign ve sirotik asit ayırıcı tanısındaki diagnostik spesifitesi %81.8 ve diagnostik sensitivitesi %89.7 olarak hesaplandı. Bu sonuçlar asit sıvısı ferritin düzeyleri ölçümünün malign ve sirotik asit ayırıcı tanısında yararlı olacağını göstermektedir. [Turk J Med Res 1994; 12(6): 236-238]*

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