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Acute liver failure secondary to malignant infiltration: A single center experience

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ABSTRACT

Acute liver failure (ALF) requires early and very precise treatment decisions for a diagnosis that is not often easy and may lead to erroneous decisions. Accordingly, we undertook a review of ALF secondary to malignant infiltration given the rarity of the condition, plus its singularity and therapeutic implications. This review should aid in establishing future frameworks for action. Analyze cases of ALF secondary to malignant infiltration in our center during the last 5 years and review the literature. We undertook a retrospective review of all cases of ALF due to malignant infiltration in our center between January 2015 and December 2019. Data were recorded on demographic characteristics, clinical presentation, type of tumor, diagnostic techniques used, treatment and evolution. We also undertook a literature review on the subject and compared the results. AFL secondary to malignant infiltration was diagnosed in five patients, four women and one man with a median age 58 years. The most common clinical presentation was jaundice. Three cases were due to infiltration by hematological tumors (non-Hodgkin lymphoma and histiocytosis), one a cholangiocarcinoma and one lung cancer. In all cases a liver biopsy was required for diagnosis, this being conclusive in four cases; diagnosis in the non-conclusive case was by analysis of the hepatectomy sample after transplantation. Three patients died due to AFL in a mean of 13.8 days, another died 5 months after diagnosis as a consequence of the tumor while the patient with a diagnosis of non-Hodgkin lymphoma and transplant recipient remains alive after a follow-up of 6 years and after receiving chemotherapy. AFL due to malignant infiltration is a very unusual condition but with a high rate of mortality. It requires a rapid and precise diagnosis given the relevant treatment options.

Introduction

Acute liver failure (ALF) is a potentially severe disease, characterized by acute alteration in liver function parameters in the absence of chronic liver disease, associated with the development of coagulopathy of hepatic etiology and alteration in the level of consciousness due to hepatic encephalopathy [1].

The most frequent cause of ALF in the world (especially in Asia and Africa) is viral hepatitis (mainly A, E, and B). Nevertheless, the etiology varies according to the geographic area. In Europe the most common cause is drug-induced toxicity, while in the United States it is liver damage induced by paracetamol, and in Spain it is HBV hepatitis [1,2].

Key Points

Acute liver failure (ALF) due to malignant infiltration:

- A very unusual entity that is difficult to diagnose.
- May be the clinical presentation of an undetected cancer.
- Should be suspected if there is a prior history of cancer or massive hepatomegaly of unknown cause.
- Causative tumors are more often hematologic than solid tumors.
- Needs a precise, early, etiologic diagnosis to start adequate treatment.
- Imaging tests (echo, CT, and MR) often fail to provide a diagnosis.
- Liver biopsy is a fundamental diagnostic test, although it may occasionally be inconclusive.
- Liver transplantation is a formal contraindication.
- The short-term prognosis is poor.
- The existence of multicenter registries of ALF could aid its understanding, given its rareness and the little scientific available.

Abbreviations: ALF, Acute liver failure; CT, contrast-enhanced computed tomography; MR, magnetic resonance.

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ALF is associated with a high rate of morbidity and mortality. Prior to the transplant era survival was below 15%, though now short-term survival after transplantation is estimated to be above 65% [3]. In fact, liver transplantation is the only definitive treatment option when supportive measures in intensive care units fail. It is, though, difficult to predict which patients might benefit from it, with up to 25% of patients in US experiencing greater immediate morbidity and mortality than after undergoing a transplant for other etiologies [3].

Even though the liver is the most frequent site for hematogenous dissemination of malignant tumors, malignant hepatic infiltration is a very unusual cause of liver failure, representing in the largest series 0.44%–1.4% of all cases of ALF [4,5]. Likewise, ALF as the presenting form of cancer is also very uncommon though it is associated with a very poor prognosis. Amongst reported cases, a prior history of cancer was not found in over 50% of cases of ALF due to malignant infiltration [5,6]. Different tumors can trigger this entity, including tumors of the gastrointestinal tract, lung, breast,

Table 1
Published series.

Reference	n	Tumor type	Early/Late diagnosis	Prior history of tumor	Mean time to death
Rich[4] 27 (1.4%) of 1910 cases of ALF from 23 centers were attributed to cancer	27	• 11 Leukemia/lymphoma (11) • Breast cancer (8) • Renal cell carcinoma (2) • Signet ring carcinoma (1) • Uterine carcinoma (1) • Prostate cancer (1) • Thyroid cancer (1) • Pancreatic cancer (1) • Microcytic lung (1)	• Liver biopsy before death (16) • Bone marrow biopsy (2) • Liver transplant (2)	• Yes (11) • No (16)	• 10.5 d
Rowbotham[5] 18 (0.44%) of 4020 cases of ALF in a registry analysis were attributed to cancer	18	• Non-Hodgkin lymphoma (9) • Hodgkin Disease (3) • Metastatic carcinomas (4) • Hemophagocytic syndrome with no clear precipitating cause. (2)	• Early (15) • Late (3)	• No	• 6 d
Alexopoulou[6]	5	• Carcinomas / Solid tumors	• Early (1) • Late (4)	• No	• 7 d
Harrison[7]	3	• Microcytic lung cancer	• Late	• No	• 6 d
McGuire[8]	4	• Microcytic lung cancer	• Early (1) • Late (3)	• No	• 5 d
Rajvanshi[9]	2	• Lung cancer • Lymphoma	• Late	• No	–
Hanamornroongruang[10]	1	• Breast cancer	• Early	• Yes	• 21 d
Te[11]	1	• Malignant melanoma	• Early	• No	• 7 d
Ahmadi[12]	1	• Diffuse B-cell lymphoma	• Late	• No	• 8 d
Kapuria[13]	1	• Diffuse large B-cell lymphoma	• Early	• No	• Complete remission at 6 mo
Dellon[14]	1	• Leukemia • NK T-cell lymphoma	• Early	• No	• 12 d
Guerreiro [15]	1	• Microcytic lung cancer	• Late	• No	• 7 d
Athanasakis[16]	1	• Microcytic lung cancer	• Early	• No	• 5 d
Scheneider[17]	1	• Breast cancer	• Early	• No	• 5 d
De Castro[18]	1	• Choroidal melanoma	• Early	• Yes	• 12 d
Sawabe[19]	1	• Stomach cancer	• Late	• Yes	• 4 d
Bernardo[20]	1	• Breast cancer	• Late	• Yes	• 4 d
Lee[21]	1	• Melanoma	• Early	• Yes	• 7 d
Van Marcke[22]	1	• Lung cancer	• Early	• Yes	• 4 d
Serra[23]	1	• Urothelium	• Early	• No	• 6 d
Borja[24]	1	• Breast cancer	• Late	• No	–
Esfahani[25]	1	• Chronic lymphoid leukemia	• Late	• Yes	• 48 d

RCC renal cell carcinoma.

Table 2
Characteristics of our five patients.

Patient	1	2	3	4	5
Sex	Female	Female	Male	Female	Female
Age	59	58	25	58	50
Primary tumor	Lung cancer	Mantle cell non-Hodgkin lymphoma	Large B-cell lymphoma rich in T cells and histiocytosis	Cholangiocarcinoma	Diffuse large B-cell non-Hodgkin lymphoma
Immunohistochemistry	• TTF1 • Cytokeratin 7, Cytokeratin20 • CDX2 • GATA-3 • Mammaglobin	• CD 20 • PAX5 • CD79a • BCL2 • CD43 • Cyclin D1 • CD5 positive	• Small T cells with isolated blasts CD20+BCL6+PAX5+CD79A+CD10	• Positive for PAS-diastase, k7, emacd34, k903, cd34	• CD10 negative, MUM-1 positive
Initial symptom	Jaundice	Jaundice	Jaundice	Jaundice	Ascites
Prior history of cancer	No	No	No	No	No
Tumor markers	• Elevated CA-125	• Elevated β2-microglobulin • Elevated CA-125	• Negative	• ?	• ?
Imaging tests (echography/CT)	• Hepatomegaly • Ascites	• Splenomegaly	• Splenomegaly • Ascites	• Splenomegaly • Ascites	• Splenomegaly
Diagnostic method	Biopsy	Biopsy	Hepatectomy	Biopsy	Biopsy
Moment of diagnosis respect to death or transplant	After	Before	After	Before	Before
Evolution	Died	Survived 5 mo. Death from other cause	Survival to date of 6 yr, free of disease with normal functioning graft	Died	Died
Evolution time (days)	11	31	7	11	9

thyroid, melanoma, and hematologic diseases (non-Hodgkin lymphoma, Hodgkin disease, leukemia, and malignant histiocytosis) (Table 1). This makes diagnosis difficult and it needs to be quickly and correctly recognized to avoid delays and inadequate treatment that may worsen the already poor prognosis of this condition.

Our aim was to review the cases of AFL secondary to malignant infiltration in our center in recent years, as well as to undertake a review of the literature to try to establish possible guidelines of action.

Methods

We undertook a retrospective review of all cases of ALF due to malignant infiltration in our center during the period January 2015 to December 2019. Data were recorded on the demographic characteristics, clinical presentation, type of tumor, diagnostic methods used, therapy and evolution. In addition, we searched PubMed for articles in English using the terms “acute liver failure” and “malignant infiltration” and examined the results.

Results

Demographic characteristics

During the study period there were five patients with ALF secondary to malignant infiltration, four women and one man, with ages ranging from 25 to 60 years (mean 50, median 58 years). In three cases the etiology was a hematologic tumor (non-Hodgkin lymphoma and histiocytosis) and in the other two it was a solid tumor (cholangiocarcinoma and lung cancer) (Table 2).

Clinical characteristics and laboratory tests

The form of clinical presentation was jaundice in four patients and edema-ascites decompensation in the other. No patient had a prior history of cancer. The laboratory tests all showed a rise in alkaline phosphatase, gamma glutamyl transferase and hyperbilirubinemia with coagulopathy (increased INR). The patient with lung cancer had an increased CA-125 and one of the patients with non-Hodgkin lymphoma presented with elevated β2-microglulin and CA-125. The tumor markers in the other patients were negative.

Diagnostic procedure

The imaging tests (ultrasound, CT, and MR) were not conclusive in any of the cases, with nonspecific findings of hepatosplenomegaly and ascites. In all cases a liver biopsy was necessary, which was done by transjugular approach given the coagulopathy noted by the laboratory tests. In one case the result of the liver biopsy was inconclusive so that, given the situation of fulminant AFL, a transplant was performed under Code 0. Examination of the hepatectomy sample with specific immunohistochemical techniques showed malignant infiltration due to lymphoma. In three cases diagnosis was achieved early and in one case we learned the result of the biopsy after the patient died.

Clinical evolution

Four of the five patients died (80%), three due to acute liver failure. The fourth patient who died survived for 5 months on treatment with rituximab and 3 cycles of CHOP (cyclophosphamide-doxorubicin-vincristine-prednisone), dying due to the underlying tumor. The patient who received a transplant had it on the seventh day and experienced a favorable course with a normal-functioning graft and a disease-free survival to date of 6 years. After the transplant he received CHOP chemotherapy and rituximab for 8 months to treat the lymphoma, achieving complete remission. Table 2 summarizes the main characteristics of the five patients.

Review of the literature

Malignant infiltration of the liver as a cause of ALF is rare. An exhaustive literature reviews only brought to light a few retrospective case series with just a few patients or reports of isolated cases. The largest series is that of Rich et al. [4] who undertook a multicenter study comprising 23 centers and found 1,910 cases of ALF, of which just 27 (1.4%) were attributed to a cancer, 11 of these being a hematologic cancer. The second largest series is that of Rowbotham et al. [5] who analyzed a registry of 4,020 patients with ALF, of whom just 18 (0.44%) were attributed to malignant infiltration. In this series 12 cases were associated with infiltration by lymphoma. In the series of five cases of Alexopoulou et at. [6] all the cases were due to solid tumors. Harrison et al. [7] and McGuire et al. [8] reported three and four cases (respectively) of ALF secondary to hepatic involvement from microcytic lung cancer. The other cases were all isolated cases, involving cancer of the breast, stomach, kidney urothelium, or melanoma, among others. They are shown in Table 1, [4–25].

Discussion

Malignant infiltration of the liver should be considered in the differential diagnosis of ALF of uncertain origin as it will determine the therapeutic management. The only treatment that can improve the prognosis of this entity (ALF) is liver transplantation, which itself is determined by strict indications [3,26,27].

Various mechanisms have been described in the etiopathogenesis of ALF secondary to malignant infiltration. Tumor infiltration of the bile duct, circulation and hepatic parenchyma have been suggested to produce cholangitis, ischemia and hepatocellular necrosis [28]. In addition, the rapid replacement of large areas of liver parenchyma by malignant cells can result in massive destruction of hepatocytes and the ensuing ALF. Another mechanism causing liver hypoxia can be the release of cytokines by tumor cells, especially in hematologic cancers, which produces damage in the bile canaliculi and activation of leukocytes and sinusoidal cells that prevent sinusoidal microcirculation [29]

As seen in the literature reviewed and in agreement with our results, the most common tumor types found were hematologic tumors, like Hodgkin and non-Hodgkin lymphoma, acute leukemia, acute transformation of chronic leukemia and other lymphoproliferative syndromes such as histiocytosis or chronic lymphoid leukemia [4,5,25]. Solid tumors are less common, but include those of the gastrointestinal tract, breast, lung, and melanoma, among others. Table 1.

The predisposition to microscopic hepatic infiltration by lymphoproliferative syndromes and the development of ALF could be explained by the role played by the cytokines in these tumors. The massive release of cytokines from lymphomatous cells can destroy the bile duct and cause portal fibrosis. Interleukin 2 in particular induces hepatotoxicity, activating the Kuppfer cells with the release of other cytokines that produce platelet adhesion to the sinusoidal endothelium and impede the hepatic microcirculation, producing ischemia [30].

The mean age of our patients was 50 years and most (4/5) were women, data similar to those reported in other series [4,5].

ALF secondary to malignant infiltration requires a high degree of suspicion, especially in the absence of any previous tumor, as the presenting form is nonspecific. In our series, as in most of the cases reported (Table 2), there was no prior history of cancer, which represents a diagnostic difficulty. The initial symptom in most of our patients was jaundice and the laboratory tests showed alteration in the liver profile and coagulopathy, as in ALF for other causes. The imaging tests were not conclusive given the absence of space-occupying lesions in the liver due to the microscopic infiltration pattern [6]. However, all of our patients presented hepatomegaly, so that its presence in a patient with ALF of unknown origin should lead one to suspect a possible malignant infiltration, especially once a viral or toxic etiology have been discarded.

In some of our patients we detected a rise in tumor markers (CA-125 and β2-microglulin), as also found in some of the other cases reported. Accordingly, their measurement should always be considered during the etiologic study of ALF.

These factors all hinder and delay the diagnosis of this entity. It is, therefore, fundamental to perform an early biopsy to confirm the histologic diagnosis, as the presence of disseminated malignancy constitutes a contraindication for liver transplantation [27]. Given the alteration in coagulation that these patients presented, biopsy is considered a procedure involving a high risk of bleeding and a transjugular approach is needed in most cases.

In our series we made an early diagnosis in three of the five patients. The other two were diagnosed late, one from the hepatectomy sample after transplant and the other postmortem. In the series of Rich et al [4] diagnosis was made by liver biopsy premortem in 16 of the 27 patients and in the series of Rowbotham et al [5] in 15 of the 18 cases. Alexopoulou et al. [6] however, were only able to make an early diagnosis in one of their five cases. As in the other series, early diagnosis in our patients was a challenge bearing in mind that liver failure was the iniktial presentation of the cancer.

In our experience, a patient with non-Hodgkin lymphoma who underwent an emergent transplant before the diagnosis made from the hepatectomy sample at the time of transplant was available currently has a disease-free survival and normal functioning graft of 6 years. Notably, in the series of Rich et al [4] one of the two patients who underwent a transplant survived for over 5 years. The few reports available describe a slightly better prognosis in patients with ALF secondary to infiltration from lymphoproliferative syndromes, mainly non-Hodgkin lymphoma, given the tendency of this type of tumor to respond favorably to chemotherapy. This contrasts to the worse prognosis after dissemination of solid tumors. In the series of Alexopoulou et al [6] which reported finding only cases with solid tumors, all the patients died within a mean of 7 days, and in the series of Rowbotham et al [5] the only patient to survive was a case of non-Hodgkin lymphoma who received chemotherapy.

Our study has certain limitations. It was a single-center retrospective study of a small series of cases undertaken over just 5 years. However, the rareness of this condition, its diagnostic difficulty and the poor short-term prognosis hindering early diagnosis partly explain these limitations, together with the scarce evidence available in the relevant literature. Nevertheless, the more than 25 years of experience of our multidisciplinary team with over 1000 liver transplants endorse our producing this update.

Conclusions

Acute liver failure, although uncommon, may be the initial manifestation of cancer. Its identification requires a high degree of suspicion and an exhaustive study. Tumor etiology should form part of the differential diagnosis of ALF. Histologic diagnosis is fundamental as the presence of disseminated malignancy currently constitutes a contraindication for liver transplantation. The TEXT BOX gives the key considerations to bear in mind.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

CRediT authorship contribution statement

Rocío González Grande: Conceptualization, Methodology. **Ana Bravo Aranda:** Data curation, Writing – original draft. **Inmaculada Santaella Leiva:** Visualization, Investigation. **Susana López Ortega:** Visualization, Investigation. **Miguel Jiménez Pérez:** Supervision, Conceptualization, Methodology, Validation, Writing – review & editing.

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