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Original contribution

Frequency and pathological characteristics of drug-induced liver injury in a tertiary medical center☆

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Summary Drug-induced liver injury (DILI) accounts for approximately 10% of acute hepatitis cases. DILI can arise as idiosyncratic or intrinsic injury from hundreds of drugs, herbals, and nutritional supplements and is essential to recognize as one of the differential diagnoses of hepatitis in a liver biopsy. The purpose of this study is to investigate the frequency and pathological characteristics of DILI related to the variety of hepatotoxic agents. We searched our pathology database for all patients with hepatitis diagnosed on liver biopsy from January 2012 to May 2016, and selected patients with a diagnosis of DILI. Electronic medical records were reviewed for patient medication list, history of herbal medicine or supplement use, and pre-biopsy liver function test (LFT) results. Clinical and pathologic correlation was used to determine the causative or related agents for DILI. We then assessed histopathologic features of liver injury and categorized biopsy findings as primarily bile duct injury, lobular/portal hepatitis, or mixed changes. Six hundred four total liver biopsies for hepatitis or liver injury were identified, of which 70 cases (11.6%) carried the diagnosis of DILI confirmed by clinical correlation. The most common etiologies associated with DILI were supplements and herbal products (31.4%), antimicrobials (14.3%), chemotherapeutics (11.4%), antilipidemics (7.1%) and immunomodulatory agents (7.1%). LFT results positively correlated with histological findings. Nutritional/herbal supplements have emerged as one of the major hepatotoxicity agents. DILI can manifest as predominantly hepatitis, bile duct injury or combination. Histological pattern recognition in the liver biopsy may help identify specific hepatotoxic agents causing DILI.

1. Introduction

The annual incidence of drug-induced liver injury (DILI) is 19.1 per 100 000 according to a recent large epidemiologic study [1]. DILI can arise as either idiosyncratic or intrinsic injury from hundreds of drugs, herbals, and nutritional supplements. Idiosyncratic DILI is unpredictable and occurs only in a minority of individuals taking the same drug or supplement product at the same dose, while intrinsic DILI is predictable and dose-dependent [2]. In the United States, idiosyncratic DILI was found to account for approximately 11% of all cases of acute liver failure [3]. It represents the overwhelming majority of cases of DILI and occurs from varied etiologic agents. The agents responsible for DILI are documented by large

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national registries such as the U.S. Drug-Induced Liver Injury Network (DILIN) [4].

Diagnosis of DILI depends on clinical, laboratory, and most times, histological examination. When clinically suspicious, liver function tests (LFTs) can be the first line of evidence of DILI. LFTs can show a predominant hepatocellular (52%), cholestatic (25%), or mixed (23%) pattern of biochemical liver injury, categorization based on the R-ratio, or ratio of alanine aminotransferase (ALT) to alkaline phosphatase (ALP) [5,6]. Liver biopsy is essential for an accurate diagnosis in the majority of cases. Histologically, most DILI can be categorized as acute and chronic cholestatic, acute and chronic hepatitis or mixed hepatitic-cholestatic pattern of injury [7]. However, the histologic and biochemical categorization of liver injury does not perfectly correlate as cholestatic and bile duct injury is often underestimated by ALP levels; however, elevated ALT does predict histologic hepatocellular damage [7]. The purpose of this study is to investigate the frequency and pathological characteristics of DILI related to a variety of hepatotoxic agents and correlate histology to biochemical categorization at a single major medical institution, to aid in accurate diagnosis.

2. Materials and methods

2.1. Patients

We first determined the overall number of biopsy-proven hepatitis cases at our institution by searching the pathology database using the search terms "hepatitis" and "injury" from January 2012 to May 2016. Among these cases, DILI cases with pathology diagnosis were identified by searching the phrases "liver and drug," "liver and medication," "liver and herbal," and "liver and supplement". Of the cases identified by this initial search, medical records were reviewed for all patients with pathology "likely," "possible/probable," "favoring" or "consistent with" the diagnosis of DILI. The medical records were reviewed for past medical and surgical history, patient medication list, and history of herbal medicine or nutritional supplement use. LFT results including ALT, aspartate aminotransferase (AST), ALP and total bilirubin were also collected using the first results obtained, which qualified as indicative of DILI.

The causative relationships were established according to Roussel Uclaf Causality Assessment Method (RUCAM) [8,9]. The RUCAM score is a point-based system in which points are given for time of onset, course of illness, concomitant drugs, liver injury risk factors and other possible causes of liver injury, and previous information on hepatotoxicity of a drug, in addition to response to readministration if available. The point total is used to determine how likely it is that a drug caused liver injury. A drug is excluded from causing DILI if there are no points, and if there are any points in favor of possible drug injury then it is defined as "unlikely," "possible," "probable" and "highly probable" in terms of increasing likelihood that the drug is responsible for liver injury. All cases where DILI was considered to be at least "unlikely" according to this scale were included.

To define the DILI biochemically, we used the RUCAM score to determine whether the hepatic injury is "hepatocellular," "mixed," or "cholestatic." This assessment was done using R-ratio, defined as (ALT/upper limit of normal [ULN] ALT)/(ALP/ULN ALP). Results of 0 to 2 (or an increase in ALP ≥2× ULN with normal ALT) were "cholestatic," 2 to 5 were "mixed," and >5 (or an increase in ALT ≥2× ULN with normal ALP) were "hepatocellular" injury pattern; for those results where only one of ALT or ALP was elevated, the injury was defined according to the elevated lab result regardless of ratio [8,9]. Agents responsible for DILI were then grouped into following categories: antimicrobial agents, psychotropics (including antipsychiatric drugs as well as neuron-targeting drugs), chemotherapeutics, antilipidemics, nonsteroidal anti-inflammatory drug (NSAIDs), immunologic agents, endocrine agents, antihypertensive agents, anti-gastritis agents and herbals/nutritional supplements.

2.2. Histological examination

Glass slides for all cases were reviewed by two gastrointestinal pathologists. We recorded histopathologic features of liver injury including bile duct injury, bile duct reaction, portal inflammation, interface hepatitis, lobular inflammation, fibrosis, necrosis, steatosis, steatohepatitis, presence of granulomas, and degree of plasma cell and eosinophilic infiltrate. The changes were graded on a semiquantitative scale from 0 to 3, and fibrosis was staged from 1 to 4 [10]. Plasma cells and eosinophils were classified based upon the highest number of cells per high-power field (HPF): 0 if no cells were present; 1+ for <5; 2+ for 5 to 10; and 3+ for >10 cells. Histopathologic findings were then categorized as primarily cholestatic injury, hepatocellular injury, or mixed changes based on the relative

Table 1 Frequency of various causes of DILI

Drug category	Number of cases	Frequency as percentage of all DILI cases (%)	Frequency as percentage of all hepatitis cases (%)
Supplement	22	31.4	3.6
Antimicrobial	10	14.3	1.7
Chemotherapy	8	11.4	1.3
Antilipidemic	5	7.1	0.8
Immunomodulatory	5	7.1	0.8
Endocrine	4	5.7	0.7
NSAID	4	5.7	0.7
Psychotropic	4	5.7	0.7
Antihypertensive	4	5.7	0.7
Anti-gastritis	3	4.3	0.5
Other drug (allopurinol)	1	1.4	0.2
All DILI cases	70	–	11.6
All hepatitis cases	604	–	–