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Herbal hepatotoxicity: Difficulties in the diagnosis and treatment of liver lesions by borage oil

Hepatotoxicidade por ervas: Dificuldades no diagnóstico e manejo das lesões hepáticas por óleo de borragem

Hepatotoxicidad a base de hierbas: Dificultades para diagnosticar y tratar la lesión hepática por aceite de borraja

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Abstract
Introduction: The use of herbal medicines has increased over the past 20 years as a complementary therapy for various diseases. However, the commercialization of these products is not preceded by a guarantee of safety. This article aims to report the use of borage oil or *Borago officinalis* (BO), beneficial for menopause-related symptoms, however, it may contain pyrrolizidine alkaloids (AP), a hepatotoxic toxin. Methodology: a study of the patient's electronic medical record was conducted. Case report: 53-year-old woman admitted to emergency room with jaundice, asthenia, hyporexia and pain in the right hypochondrium (HD) for 10 days after use of the herbal medicine Niolix® (BO), being initially diagnosed with acute hepatitis induced by BO. Liver biopsy revealed intense lymphocyte inflammatory infiltrate, in addition to plasma cells, neutrophils and macrophages, with aggression to the limiting plaque and hepatocytes. After the end of the corticosteroid treatment, there was a new increase in aminotransferases and the appearance of autoantibodies, leading to the hypothesis of autoimmune hepatitis triggered by BO. Immunosuppressive treatment was instituted, with significant improvement in the condition. Conclusion: this report exemplifies the diversity of liver lesions induced by herbs, as well as drugs, supplements, and medications, calling attention to the strict follow-up of cases, with possible changes in diagnosis and conduct during treatment.
Keywords: Borago officinalis; Hepatitis, Autoimmune; Chemical and Drug Induced Liver Injury; Phytotherapeutic Drugs.

Resumo
Introdução: O uso de fitoterápicos aumentou nos últimos 20 anos como terapia complementar para várias doenças. No entanto, a comercialização desses produtos não é precedida de garantia da segurança. O objetivo deste artigo é apresentar o relato da utilização de óleo de borragem ou *Borago officinalis* (BO), benéfico para sintomas relacionados à menopausa, porém, pode conter alcalóides pirrolizidínicos (AP), uma toxina hepatotóxica. Metodologia: realizado

estudo do prontuário eletrônico da paciente. Relato de caso: Mulher de 53 anos deu entrada no pronto socorro com icterícia, astenia, hiporexia e dor em hipocôndrio direito (HD) há 10 dias, após uso do fitoterápico Niolix® (BO), sendo diagnosticada inicialmente com um quadro de hepatite aguda induzida por BO. A biópsia hepática descreveu intenso infiltrado inflamatório linfocitário, além de plasmócitos, neutrófilos e macrófagos, com agressão à placa limitante e aos hepatócitos. Após o fim do tratamento com corticoide, apresentou nova elevação das aminotransferases e surgimento de autoanticorpos, levando à hipótese de hepatite autoimune desencadeada por BO, sendo instituído o tratamento imunossupressor, com importante melhora do quadro. Conclusão: Esse relato exemplifica a diversidade das lesões hepáticas induzidas por ervas, bem como drogas, suplementos e medicamentos, chamando atenção para o seguimento rigoroso dos casos, com possíveis mudanças de diagnóstico e conduta no decorrer do manejo.
Palavras-chave: Borago officinalis; Hepatite Autoimune; Doença Hepática Induzida por Substâncias e Drogas; Medicamento Fitoterápico.

Resumen

Introducción: El uso de hierbas medicinales ha aumentado en los últimos 20 años como terapia complementaria para diversas enfermedades. Sin embargo, la comercialización de estos productos no va precedida de una garantía de seguridad. El objectivo de este informe es abordar el caso de uso del aceite de borraja o Borago officinalis (BO), beneficioso para los síntomas relacionados con la menopausia, sin embargo, puede contener alcaloides de pirrolizidina (PA), una toxina hepatotóxica. Metodología: se realizó un estudio de la historia clínica electrónica del paciente. Reporte de caso: Mujer de 53 años de edad, ingresó a urgencias con ictericia, astenia, hiporexia y dolor en hipocondrio derecho (DH) de 10 días de evolución, luego de utilizar la medicina herbaria Niolix® (BO), siendo diagnosticada inicialmente con hepatitis aguda inducida por BO. La biopsia hepática describió un intenso infiltrado inflamatorio linfocitario, además de células plasmáticas, neutrófilos y macrófagos, con agresión a la placa limitante y hepatocitos. Tras finalizar el tratamiento con corticoides presentó un nuevo aumento de aminotransferasas y aparición de autoanticuerpos, lo que hizo sospechar de hepatitis autoinmune desencadenada por BO, por lo que se instauró tratamiento inmunosupresor con mejoría significativa del cuadro. Conclusión: Este informe ejemplifica la diversidad de lesiones hepáticas inducidas por hierbas, así como por fármacos, suplementos y medicamentos, llamando la atención sobre el seguimiento riguroso de los casos, con posibles cambios en el diagnóstico y la conducta durante el manejo.
Palabras clave: Borago officinalis; Hepatitis Autoinmune; Enfermedad Hepática Inducida por Sustancias y Drogas; Medicamento Fitoterápico.

1. Introduction

Autoimmune Hepatitis (AIH) are chronic inflammatory diseases, characterized by the presence of circulating autoantibodies, which lead to progressive liver damage. The pathogenesis is not yet fully known, however, its occurrence is associated with genetic and environmental factors, such as infections and drug use, which function as triggers for the onset of autoantibody production and establishment of the condition (Heneghan 2024; Mercado et al., 2024).

The diagnosis of AIH includes the detection of clinical, biochemical, and histopathological changes. The clinical presentation is diverse and ranges from asymptomatic to severe hepatic insufficiency. In laboratory tests, there is an increase in ALT and AST transaminases, a possible increase in gamma globulins and the presence of autoantibodies, such as anti-nuclear, anti-smooth muscle, anti-LKM1 and anti-SLA antibodies, the latter being specific for the disease. Histopathology highlights the presence of bridge necrosis, periportal hepatitis, lymphoplasmocytic infiltrate and Rosette hepatocytes (Porta et al., 2019).

Among the causes of AIH is the use of drug substances of various classes, including herbal medicines. Medicinal herbs have a millennial history of use, with a significant increase in recent years, and many patients consider them safe in relation to drugs. However, the hepatotoxicity of more than one thousand herbs and dietary supplements is already proven, which lead to symptoms analogous to acute hepatitis (Larson, 2024; Ma et al., 2024)

Borage Oil or *Borago officinalis* (BO), composed of high doses of gamma linolenic acid (GLA), has been widely consumed worldwide due to possible anti-inflammatory properties and has been used as a treatment for various pathologies such as rheumatoid arthritis, atopic dermatitis, symptoms related to menopause and diabetic neuropathy (Tasset-Cuevas, 2013). Gamma-linoleic acid (GLA) would be useful by raising the level of prostaglandin-E which leads to the increase of cyclic adenosine monophosphate (cAMP); it can also be considered a strong suppressor of TNF-α. Such a mechanism may clarify the anti-inflammatory effect of borage oil in rheumatoid arthritis (Ghasemian et al., 2016). Low-quality products may contain

pyrrolizidine alkaloids (PA), hepatotoxic and carcinogenic toxins, which can cause sinusoidal obstruction and veno-occlusive syndrome (Neuman et al., 2015).

This article aims to report the use of borage oil or *Borago officinalis* (BO), beneficial for menopause-related symptoms, however, it may contain pyrrolizidine alkaloids (AP), a hepatotoxic toxin. This is a report of a rare case of an adult patient diagnosed with autoimmune hepatitis triggered after the use of borage oil for the treatment of menopausal symptoms.

2. Methodology

Descriptive research (qualitative nature) and quantitative one (values of lab tests) case research was carried out, in the form of a study or case report (Pereira et al., 2018; Toassi & Petry, 2021).

This case report was conducted following current bioethical standards, it was submitted to the Research Ethics Committee and approved by it (CAAE 85068024.2.0000.8667; opinion Nº 7.313.431).

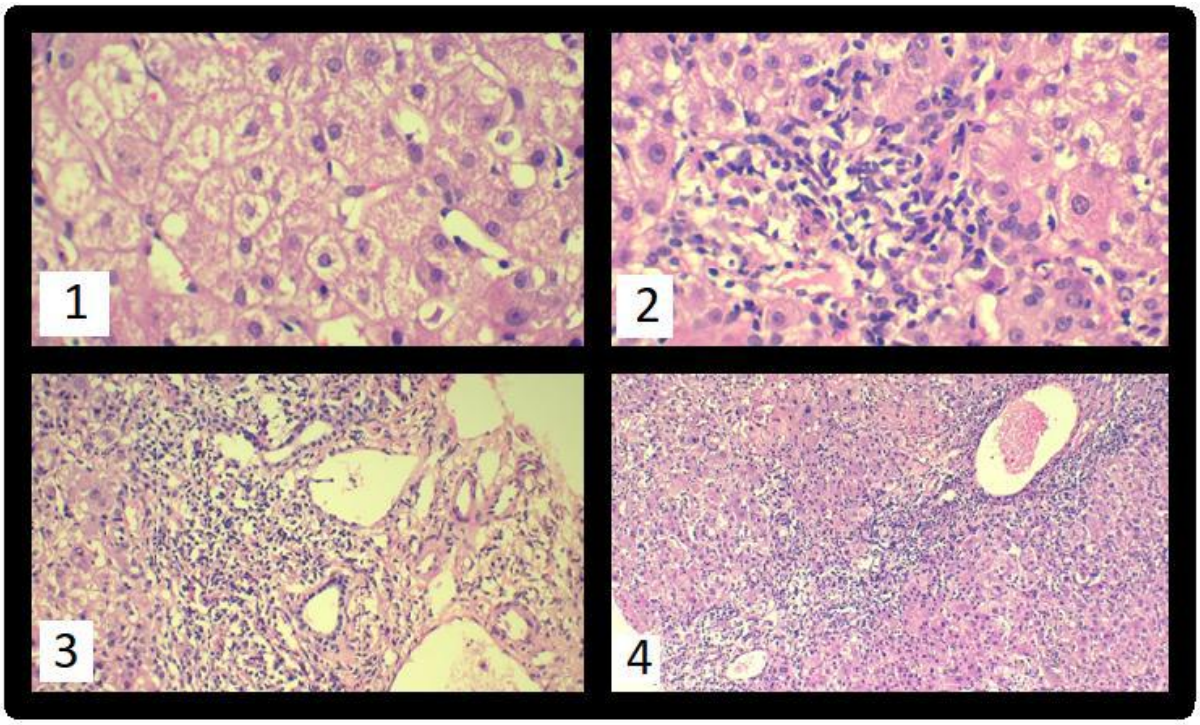
The research was conducted in 3 stages and was based on the description of retrospective data about a case of considerable rarity, through a search of the patient's electronic medical record, and an auxiliary and secondary narrative literature review (Rother, 2007; Mattos, 2015; Casarin et al., 2020), a non-systematic one, on digital platforms to correlate the bibliographic findings with the patient's condition using as search words: Borago officinalis; Hepatitis, Autoimmune; Chemical and Drug Induced Liver Injury; Phytotherapeutic Drugs.

The first stage consisted of analysis and documentation of the clinical and laboratory on the patient findings; the second stage, was the search for scientific articles about hepatotoxicity by herbs, with emphasis on BO, and autoimmune hepatitis on digital platforms such as PubMed, ScienceDirect and Google Scholar; in the third stage, the correlation of the patient's case with the findings of the literature was carried out.

3. Case Report

A 53-year-old woman was admitted to the emergency room with jaundice, asthenia, hyporexia, and pain in the right hypochondrium (HD) for 10 days. Patient symptoms began 15 days after use, for one month, of the herbal medicine Niolix® (BO) 1g/day, for menopause. On physical examination, she was dehydrated 1+/4+ and with a jaundice level of 3+/4+. At complementary examinations, she presented a hepatocellular pattern of liver damage, not evolving with signs of severe dysfunction (Table 1). Serologies for HIV, syphilis, hepatitis A, B, and C were negative. It was detected natural immunity to toxoplasmosis, cytomegalovirus, and Epstein Barr. Ruled out alpha 1-antrypsin deficiency, Wilson's disease, and hemochromatosis. In the investigation of autoimmune liver diseases, antinuclear antibodies (ANA) were identified in titration 1/160: homogeneous nuclear multiple pattern (AC-1) and homogeneous nucleolar (AC-8), immunoglobulin IgG: 2064 and electrophoresis with polyclonal increase in gamma globulins (total proteins 6.1; albumin 3.0). Non-reactive anti-mitochondria (AMA), anti-smooth muscle (ASMA) and anti-liver-kidney Type 1 (LKM1) antibodies. Liver biopsy showed intense lymphocyte inflammatory infiltrate, in addition to plasma cells, neutrophils, and macrophages, with aggression to the limiting plaque. Lobular activity, granuloma outline, isolated hepatocyte necrosis (Figure 1).

Figure 1 - Anatomopathological analysis of liver biopsy.



Source: clinical analysis and pathological anatomy unit. Clinical Hospital -UFTM (2023).

In Figure 1 (HE, 400x), it is possible to identify cellular damage resulting in hepatocyte ballooning, in response to chronic inflammation in activity, as seen in Figure 2 (HE, 400x), in which there is predominantly lymphocyte mononuclear infiltrate in the middle of the liver parenchyma (lobular activity). Periportal hepatitis is also noted (Figure 3, HE, 200x), extending to bridge necrosis (Figure 4, HE, 100x).

Without changes to imaging tests (ultrasound and cholangioresonance), the hypotheses of immune-mediated liver damage by Borago officinalis (BO) or autoimmune hepatitis triggered by the herb were raised. Started prednisone 60 mg, with slow drug weaning. After weaning from the corticosteroid, it showed a new increase in aminotransferases and autoimmunity markers remained reactive. Therefore, the hypothesis of autoimmune hepatitis triggered by BO was the most plausible and, currently, the patient is in remission, using azathioprine 1.32 mg/kg/day and prednisone 7.5 mg/day. The evolution of the laboratory results is detailed in Table 1.

Table 1 - Evolution of laboratory tests.

	05/09/23	13/09/23	19/09/23¶	17/10/23	29/12/23§	23/02/24ǂ	26/03/24	11/07/24
ALT	544	768	824	37.5	33	124	54	15.8
AST	662	742	790	27.3	33.7	74	27	23.9
Albumin	3.0	-	3.3	3.8		4.0	4.2	4.1
BT / DB	8,5/6,5	7,3/5,2	4,7/3,4	1,3/0,7	1,3/0,4	08/0,4	1,0/0,35	1,2/0,3
GGT	361	226	199	104	51.9	96	154	28.7
ALP	327	272	234	84	100.8	190	120	82
INR	1.1	1.2	1.2	-	1.0	1.0	1.0	1.0

¶ Start date of corticosteroid therapy
§ End of weaning 03/02/24
ǂ reintroduced prednisone 40 mg / day and started azathioprine 50 mg / day on 08/03/24.
Source: clinical analysis and pathological anatomy unit. Clinical Hospital -UFTM (2024).

4. Discussion

The case presented shows a patient who received the herbal borage oil in capsules as a prescription for symptoms related to menopause, and about a month after using it, developed jaundice of hepatocellular pattern and had as final diagnosis autoimmune hepatitis (AIH) triggered by BO. The pathogenesis of AIH is not fully understood and involves a complex interaction between genetic predisposition and environmental triggers with cross-reactivity with structurally similar autoantigens, leading to loss of immunotolerance (Terrabuio et al., 2020).

Many people have the false idea that when using medicinal herbs and their derivatives, they are free of adverse events because they are natural substances. Unlike drugs, which have well-described and studied composition, therapeutic action and side effects, herbal medicines and food supplements do not require broad pre-marketing approval by regulatory agencies such as the US Food and Drug Administration (FDA) or Brazil's National Health Surveillance agency (ANVISA). Thus, there is no exact standardization in the composition of such products, leading to differences between what is described on the label and what is contained in the package (National Library of Medicine, 2019).

Borago officinalis or borage is an herb cultivated for medicinal and culinary uses, although it is grown commercially for borage seed oil, which is the richest plant source of gamma-linolenic acid. GLA is sometimes prescribed as an anti-inflammatory with the belief that it does not have the common side effects of other anti-inflammatory drugs. It is also used for the treatment of multiple sclerosis, diabetes, heart disease, arthritis, eczema, autoimmune disorders, cancer, and premenstrual syndrome (Asadi-Samani et al., 2014). However, several metabolites of BO have been reported, such as resins, tannins, ascorbic acid, niacin, beta-carotene, riboflavin, silicic acid, thiamine, choline arabinose, polyphenols and unsaturated pyrrolizidine alkaloids (amabilin, lycopsamine and supinidine), in addition to numerous other compounds extracted of seeds, flowers or leaves (Ibrahim & Saheb, 2023; Smith & Culvenor, 1981)

There are reports in the specialized literature of status epilepticus associated with the ingestion of borage oil due to probable interaction with anti-convulsant drugs (Miller, 1998; Al-Khamees et al., 2011). And the possible presence of alkaloids of the pyrrolizidine group could lead to numerous other adverse effects, such as liver failure, already described in cattle (Castro et al., 2012), horses, and sheep (Santos et al., 2008). Cases of AP poisoning in humans have been reported and prolonged exposure to such alkaloids can cause human hepatic sinusoidal obstruction syndrome (Pittler & Ernst, 2003). Pyrrolic metabolites are highly reactive bifunctional alkylating agents, once formed they can quickly bind to nucleophilic groups in cellular proteins and DNA, which can result in acute and chronic hepatotoxicity, genotoxicity, and carcinogenicity (Schrenk et al., 2021; Wang et al., 2021).

The case report patient is undergoing treatment for autoimmune hepatitis, which manifested itself after the use of borage. Other triggering agents for autoimmunity were ruled out and liver biopsy was compatible with drug-induced liver injury (DILI or HILI). In the hospital where the patient is being monitored, it is not possible to perform the pharmacological analysis of the real components of the formula used and due to the presented condition, re-exposure to the product is not recommended. The US National Institutes of Health (NIH) has developed a database of dietary supplement labels with more than 192.000 products, which includes fifty-nine presentations containing BO, currently on sale in that country (Dietary Supplement Label Database, 2024).

No case like the one described was found in the literature, in which Borago or pyrrolizidine alkaloids were triggers of autoimmune hepatitis, however, it was not possible to analyze the pharmacological components that actually make up the product used by the patient. Diagnosis of herbal-induced liver injury (HILI) can be difficult. A medical history can be useful, but it is not always reliable. The relationship between exposure and liver toxicity (latency) is not always clear and is quite variable. Patients may be taking multiple preparations or products with multiple ingredients, making it impossible to identify a

single damaging agent (Larson, 2024). Pre-marketing drug testing and Pharmacovigilance are required for all herbs as well as for any other drug (Stickel et al., 2005).

5. Conclusion

The importance of the topic addressed in the report is highlighted regarding the issue of hepatotoxicity due to the use of herbal medicines. It is concluded that this case exemplifies the diversity of liver lesions induced by herbs, as well as the need for a high rate of suspicion of hepatotoxicity of drugs, supplements, and medications, calling attention to the strict follow-up of cases, with possible changes in diagnosis and conduct during treatment.

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